

**VALIDITY OF THE PORTABLE PIKO-6 SPIROMETER USED FOR
SCREENING OBSTRUCTIVE AIRWAY DISEASES IN COMMUNITY
PHARMACY PRACTICE**

by

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ABSTRACT

Background: Obstructive airway diseases (OADs) are among the leading causes of morbidity and mortality worldwide. Shortness of breath (SOB) is the main symptom associated with OADs. International guidelines from the Global Initiative for Chronic Lung Disease (GOLD) and the Global Initiative for Asthma (GINA) have recommended spirometry as an indispensable tool for the diagnosis of asthma and chronic obstructive pulmonary diseases (COPD), but spirometry is rarely used in family practice. Simple and reliable diagnostic tools are necessary for screening community patients with onset of OADs for timely management.

Purpose: This thesis examined screening utility of the PiKo-6 forced expiratory volume in one second ($pFEV_1$), in six second ($pFEV_6$), and the pRatio ($pFEV_1/pFEV_6$) in SOB patients for OADs in community pharmacy settings. FEV_6 has recently been suggested an excellent surrogate for Forced Vital Capacity (FVC), which requires maximum exhalation of the lungs.

Methods: Patients with SOB symptoms who were prescribed pulmonary inhalers, by their family physicians, were recruited via community pharmacies. Trained pharmacists collected two PiKo-6 tests to assess the repeatability of the PiKo-6 device. All patients performed laboratory spirometry (FEV_1 , FVC and FEV_1/FVC) to obtain physician diagnosis of their OADs. The results of the PiKo-6 spirometer and laboratory spirometer were compared. In addition, the PiKo-6 pRatio and laboratory FEV_1/FVC were assessed against physician diagnosed COPD.

Results: Sixty three patients volunteered to perform the PiKo-6 spirometry. Of these, 52.4 % were men (age 53.9 ± 15.3 years; BMI 31.9 ± 7.40 kg/m²). Repeated testing with $pFEV_1$, $pFEV_6$ and pRatio correlated significantly (within correlation, $r = 0.835$, $p\text{-Value} \leq 0.05$; 0.872 , $p\text{-Value} \leq 0.05$; and 0.664 , $p\text{-Value} \leq 0.05$). In addition, $pFEV_1$, $pFEV_6$ and pRatio correlated significantly with FEV_1 , FVC and FEV_1/FVC , respectively (between correlation = 0.630 , $p\text{-Value} \leq 0.05$; 0.660 , $p\text{-Value} \leq 0.05$ and 0.580 , $p\text{-Value} \leq 0.05$). The cut-off value corresponding to the greatest sum of sensitivity and specificity of pRatio for physician-diagnosed COPD was <0.80 , the sensitivity and specificity were 84 % and 50%, respectively.

Conclusions The portable PiKo-6 correlates moderately well with the standard spirometry, when delivered by community pharmacists to patients with OADs. The PiKo-6 spirometer may play a role in screening patients suspected of having an OAD in community pharmacies that may benefit from early physician diagnosis and appropriate management.

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DEDICATION

This thesis is dedicated to my parents whose endless love for me and support of my education has made it possible for me to follow this path. I also dedicate this thesis to my siblings who have supported me throughout the process. You know I couldn't have done this without you.

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List of Abbreviations

ABG: Arterial Blood Gas

ACOS: Asthma and COPD Overlap Syndrome

ACPM: American College of Preventative Medicine

ATS: American Thoracic Society

BD: Bronchodilator

BNP: Brain Natriuretic Peptide

CCHS: Canadian Community Health Survey

CCS: Canadian Cardiovascular Society

CDC: Centers for Disease Control and Prevention

CHMS: Canadian Health Measures Survey

CIHI: Canadian Institute for Health Information

COPD: Chronic Obstructive Pulmonary Disease

CRD: Chronic Respiratory Diseases

CTS: Canadian Thoracic Society

DLCO: Diffusing Capacity

ECG: Electrocardiogram

ECRHS: European Community Respiratory Health Survey

ED: Emergency Department

EPICORE: Epidemiology Coordinating and Research

EpiSOB: Epidemiology of Shortness of Breath

ERS: European Respiratory Society

FET: Forced Expiratory Time

FEV₁: Forced Expiratory Volume in one second

FEV₆: Forced Expiratory Volume in six seconds

FP: Family Physician

FRCPL: Functional Residual Capacity Plain phase

FVC: Forced Vital Capacity

GINA: Global Initiative for Asthma

GOLD: Global Initiative for Chronic Lung Disease

HF: Heart Failure

HRQL: Health-Related Quality of Life

ICC: Intraclass Correlation Coefficient

IPAG: International Primary Care Airways Group

ISAAC: International Study of Asthma and Allergies in Childhood

LAAC: Long-Acting Anticholinergic

LABA: Long-Acting Beta-Agonist

MRC: Medical Research Council

NCQA: National Committee for Quality Assurance

NHLBI: National Heart, Lung, and Blood Institute

NLHEP: National Lung Health Education Program

NPHS: National Population Health Survey

OADs: Obstructive Lung Diseases

PAH: Pulmonary Arterial Hypertension

PEF: Peak Expiratory Flow

pFEV₁: Piko-6 measure of forced expiratory volume in one second

pFEV₆: Piko-6 measure of forced expiratory volume in in six seconds

PFT: Pulmonary Function Testing

PHAC: Public Health Agency of Canada

pRatio: the ratio of $pFEV_1/pFEV_6$

R: Pearson correlation coefficient

RV: Residual Volume

ROC: Receiver Operating Characteristic

ROC-AUC: Area Under the ROC Curve.

SAAC: Short-Acting Anticholinergic

SABA: Short-Acting Beta-Agonist

SCRIP: Study of Cardiovascular Risk Intervention by Pharmacists

SD: Standard Deviation

SLCDC: Survey on Living with Chronic Diseases in Canada

SOB: Shortness of Breath

TLC: Total Lung Capacity

VA: Alveolar Volume

VC: Vital Capacity

WAP: Written Action Plans

WHO: World Health Organization

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Chapter 1: Introduction

1.1 Background and study rationale

Obstructive airway diseases (OADs) are among the leading causes of morbidity and mortality worldwide, and its prevalence has increased globally in the last few decades. International guidelines on lung diseases from the Global Initiative for Chronic Lung Disease ([GOLD], 2014) and the Global Initiative for Asthma ([GINA], 2014) have recommended the use of spirometry in pulmonary function testing (PFT) as an indispensable tool for the diagnosis of OADs. Asthma and chronic obstructive pulmonary disease (COPD) are two of the most common OADs that require spirometry for diagnosis. However, spirometers are widely inaccessible in family practice. Community patients with shortness of breath (SOB), the main symptom associated with OADs, may have been provided an unreliable diagnosis due to the underutilization of spirometry which is required to evaluate and diagnose the underlying disease (Walters et al., 2011). Portable spirometers might play a crucial role in screening community patients for adequate and timely management of OADs. The main objective of this thesis is to evaluate whether the portable PiKo-6 spirometer, obtained in community pharmacy settings, correlate well with the standard laboratory PFT.

1.2 Overview

1.2.1 Dyspnea and shortness of breath

Dyspnea refers to the sensation of difficulty in catching one's breath, simply termed shortness of breath (SOB). The American Thoracic Society (ATS) defines SOB as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in

intensity” (Meek et al., 1999). The ATS definition suggests that SOB is a complex and multidimensional concept that is subjective and may not be inferred from clinical or laboratory investigations (Parshall et al., 2012). SOB is an expected outcome of excessive physical activity; nevertheless, it is considered pathologic if it occurs during rest (Shiber & Santana, 2006). Often, patients with SOB may experience suffocation, chest tightness or difficulty in catching their breath. In most cardiopulmonary diseases, SOB is caused by both increased ventilatory demand and altered ventilatory mechanics (Parshall et al., 2012). The severity of SOB is correlated with advanced age, some occupational settings, cigarette smoking, and the presence of major cardiopulmonary diseases (Wahls, 2012; Parshall et al., 2012; Currow et al., 2009). SOB afflicts many Canadians and it remains difficult to diagnose, treat, or manage in family practice settings.

1.2.2 Epidemiology of SOB associate diseases

The prevalence of cardiopulmonary disease in Canada is rising. The public Health Agency of Canada (PHAC) estimates that 3 million Canadians are suffering from respiratory diseases (PHAC, 2007). Lung diseases have a major impact on the individual, the family, the community, and the health care system. After cardiovascular disease and cancer, chronic respiratory diseases (CRD) account for most hospitalizations and deaths (PHAC, 2007).

SOB is the single most common symptom underlying many restrictive and obstructive lung and heart diseases. Asthma, chronic obstructive pulmonary disease (COPD), pulmonary hypertension, and heart failure are known diseases which cause SOB. Table 1 presents the differential diagnosis for SOB associated diseases in community patients who presented to primary care practice in Amsterdam, Netherlands (Ponka & Kirlew, 2007). The authors assumed that the primary care populations in the Netherlands and in Canada are comparable (Ponka & Kirlew, 2007).

Table 1.1 *Percentages of the differential diagnosis of shortness of breath by age groups (under 45 years compared to over 45 years)*

Differential Diagnosis	Age Groups	
	Under 45 years	45 years and older
Asthma	31.80 %	9.90 %
Acute Bronchitis	21.50	14.70
COPD	1.50	23.70
Congestive Heart Failure	0.07	15.30
Dyspnea Not-Yet-Diagnosed	7.00	8.20
Anxiety	7.80	3.30
Upper Respiratory Infection	6.70	1.50
Pneumonia	2.50	3.30
Acute Laryngitis/Tracheitis	4.70	1.00
Ischemic Heart Disease	0.20	2.30
Lung Malignancy	0.00	1.30
Pulmonary Embolism	0.30	0.50
Other	16.00	15.00

Table adapted from (Ponka & Kirlew, 2007).

1.2.2.1 Asthma

Etiology

Asthma is an inflammatory airway disease with onset rooted in a complex set of environmental, genetic, socioeconomic, and medical factors (Ober & Yao, 2011). The Global Initiative for Asthma (GINA) defined asthma as:

“a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and intensity, together with variable expiratory airflow limitation.” (GINA, 2014).

Asthma causes an obstruction of the small airways (bronchioles) and bronchial tubes of the lungs. The disease varies in severity and frequency among individuals. During an asthma attack, the lining of the bronchial tubes swells causing the airways to narrow, reducing normal airflow in

and out of the lungs (World Health Organization [WHO], 2014). The pathogenesis of asthma is unknown, and there are no laboratory blood tests or biomarkers that definitively diagnose asthma or distinguish it from other diseases (Ober & Yao, 2011). When symptoms are not adequately controlled, it can limit the physical, emotional, and social lives of asthmatics.

Diagnosis

Clinical diagnosis of asthma is primarily based on identifying recurrent appearances of symptoms such as wheezing, SOB, chest tightness or cough, and variable expiratory airflow limitation (GINA, 2014). When in doubt, asthma is diagnosed with examination of spirometry results. Reversibility of symptoms, that improve or disappear after bronchodilator medications, is required to definitively diagnose asthma (GINA, 2014). Baseline assessment of pulmonary status can include pulse oximetry, chest radiograph, electrolyte levels, and arterial blood gas (ABG) analysis. ABG analysis may be used to test for cardiac diseases associated with SOB.

Treatment and Management

Four surveys regarding asthma in America, Europe, Asia-Pacific, and Japan highlighted that asthma is underdiagnosed and undertreated, with significant opportunity for improvements in asthma control (Braman, 2006). To et al. (2012) indicated that asthma control is not ideal in many countries and estimated that nearly half of the asthma population in the world reported wheezing in the last 12 months, but only a moderate proportion had been diagnosed and/or received treatment. Asthma management aims to decrease exacerbations, airflow obstruction, and side effects of treatment (GINA, 2014). The patient – healthcare provider partnership is crucial to achieve effective asthma management. This partnership could empower patients to take a major role in managing their asthma (GINA, 2014). Asthma can be treated and managed

by primarily using pharmacological methods; in addition, non-pharmacological methods could be beneficial in managing asthma.

Currently, there is no cure for asthma, but appropriate assessment and management using pharmacologic treatments to control asthma may prevent frequent exacerbation and enhance a patient's quality of life. GINA recommends that every patient with asthma should have a reliever medication, and most adults and adolescents with asthma should have a controller medication (GINA, 2014). Spirometry examinations are usually repeated to assess the efficacy of the medication. In addition to medications, non-pharmacological strategies and interventions may be considered to manage asthma symptoms and exacerbations. These strategies include: promoting smoking cessation, improving physical activity, and removing occupational sensitizers (GINA, 2014). There are many types of triggers or allergens such as tobacco smoke, stress, and physical exercise. To avoid frequent asthma exacerbations, it is recommended that patients recognize and avoid what triggers their asthma (WHO, 2013).

Written Action Plans (WAP) are a set of tailored instructions designed to help a person with asthma to understand their worsening symptoms and the response required. GINA recommends that asthmatic patients should be provided with a WAP, appropriate for their level of asthma control and health literacy, which include: the patient's usual asthma medications, when and how to increase medications, and how to access medical care if symptoms fail to respond (GINA, 2014). Unfortunately, evidence suggests that as few as 25% of eligible patients receive WAPs from their physician or other health care professionals (Rank et al., 2008).

Prevalence and Incidence Rates

Worldwide: According to the World Health Organization (WHO), about 235 million people currently suffer from asthma; in addition, it is the most common non-communicable disease among children (WHO, 2013). In a review of 178,215 adults in 70 countries, asthma

continues to be a major public health concern globally, despite differences in income status between countries (To et al., 2012).

Canada: The Public Health Agency of Canada (PHAC) stated that asthma accounts for approximately 80% of chronic respiratory diseases nationally (PHAC, 2007). Statistics Canada (2013) reported approximately 7.9% of the population (aged 12 and over), roughly 2.4 million people, have been diagnosed by a health professional as having asthma (Statistics Canada, 2013). A study has been conducted in Ontario to calculate the annual asthma incidence rate from 1996 to 2005 (Gershon, Guan, Wang, & To, 2010). Gershon et al. stated that asthma incidence rates increased in children by 30% and were relatively stable in adults (Gershon, Guan, Wang, & To, 2010).

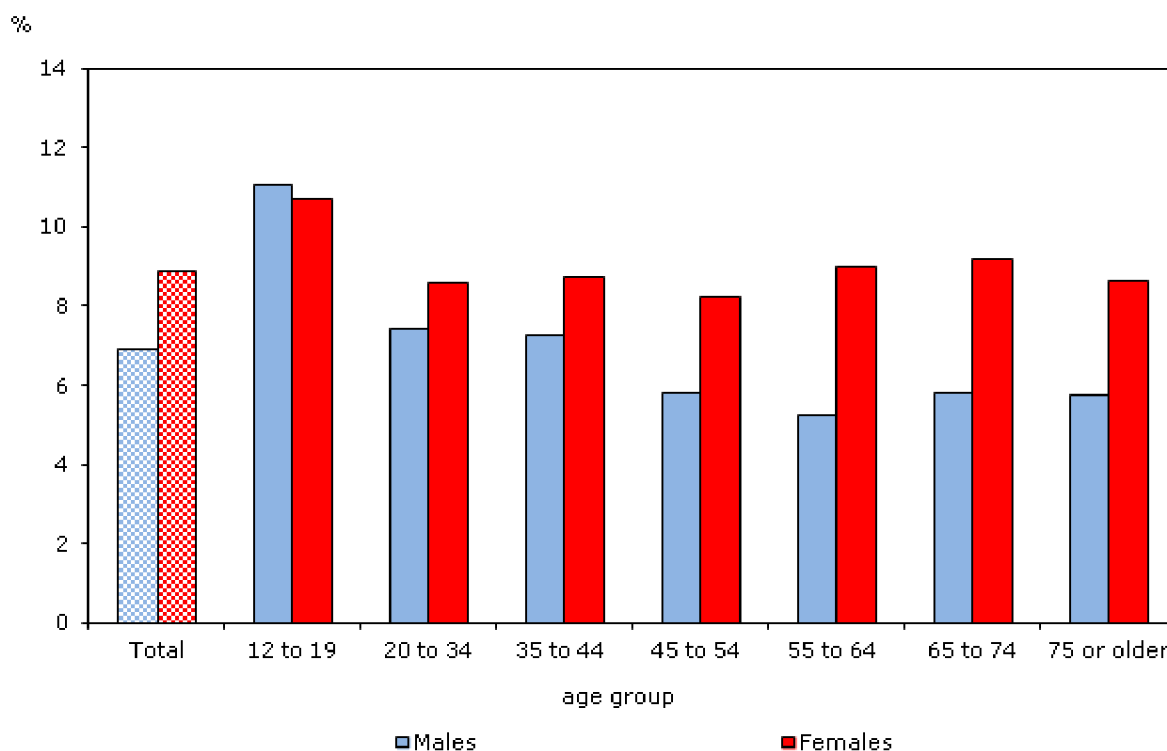


Figure 1.1: Prevalence of physician-diagnosed asthma by age and sex. Canada, 2013

In 2013, Statistics Canada reported the percentage of population aged 12 and over, who reported that they have been diagnosed by a health professional as having asthma. The percentage with asthma was 8.8% in Alberta, 7.3% in Saskatchewan, and 8.2% in Newfoundland (Statistics Canada, Canadian Community Health Survey[CCHS], 2013). Between 2001 and 2013, females (8.9%) were more likely than males (6.9%) to report that they had asthma. Figure 1.1 shows that asthma prevalence changes as the population ages. The high prevalence in young boys is not maintained into adulthood. The highest prevalence in females is during adolescence and it remains higher than males into adulthood (Statistics Canada, 2013).

Epidemiological Challenges

In epidemiological studies, measuring prevalence and incidence of asthma presents a challenge due to the evolving definition and the inconsistent use of clinically objective measurements for diagnosis. It is difficult to compare the results from different studies due to the differences in the definitions currently available (To et al., 2012; Jia et al., 2013). Furthermore, the symptoms of asthma are nonspecific and have multiple differential diagnoses. Another reason for the epidemiology challenges when studying asthma is the lack of a gold-standard diagnostic test (Sears, 2014). Increased exposure to indoor allergens and poor air quality are some of the factors that increased asthma prevalence (American College of Preventative Medicine [ACPM], 2013). Although urbanization is correlated with an increased risk of asthma incidence, the nature of the risk is unclear (Robinson et al., 2011).

Economic burden

Morbidity from asthma can be defined in several ways: asthma exacerbations, physician visits, emergency department (ED) visits, and hospitalizations. ED visits and hospitalization due to asthma causes a significant economic burden on the health care system. The WHO (2014) stated that the global cost of asthma is estimated to surpass the combined cost of tuberculosis and

acquired immune deficiency syndrome. Among patients presenting to the ED for acute asthma treatment in Canada, 51% reported having an unscheduled visit in the previous year and 30% reported having one or more ED visits per year (Rowe et al., 2010). The Conference Board of Canada stated that the combined direct and indirect costs of asthma would increase from \$2.2 billion in 2010 to about 4.2 billion by 2030 (Thériault, et al., 2012).

Mortality

Approximately 250,000 people die prematurely each year from asthma, and most of these deaths are avoidable (WHO, 2007). In Canada, asthma mortality in one year averages approximately 250 people (Conference Board of Canada, 2012). Despite advances in understanding of the disease, several factors have been linked to asthma deaths. Omachi et al. stated that greater severity-of-asthma scores and poorer perceived asthma control scores were each associated with increased mortality risk among adults with severe asthma (Omachi et al., 2008).

1.2.2.2 Chronic Obstructive Pulmonary Disease

Etiology

It refers to a group of lung diseases that include chronic bronchitis and/or emphysema. COPD is directly related to the prevalence of smoking (Global initiative for chronic Obstructive Lung Disease [GOLD], 2014). GOLD defined COPD as:

“ a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients” (GOLD, 2014).

This indicates that the etiology of COPD involves a complex set of genetic determinants, lung injury due to excessive smoking, and environmental stimuli (Decramer, Janssens, & Miravittles, 2012). Elbehairy et al., stated that COPD is associated with extensive impairment of small airway function, progressive morbidity and reduced life-expectancy (Elbehairy, Webb, Neder, & O'Donnell, 2013).

Diagnosis

The Global initiative for chronic Obstructive Lung Disease (GOLD) stated that a clinical diagnosis of COPD should be considered in any patient who has SOB, chronic cough or sputum production, family history of COPD and a history of exposure to risk factors of the disease, such as: tobacco smoke, smoke from home cooking and heating fuels, and occupational dusts and chemicals (GOLD, 2014). Spirometry is the primary diagnostic tool for COPD. Forced Expiratory Volume in one second (FEV_1) is the volume exhaled during the first second of a forced expiratory maneuver started from the level of total lung capacity. Forced Vital Capacity (FVC) is the amount of air which can be forcibly exhaled from the lungs after taking the deepest breath possible. The presence of a post- bronchodilator $FEV_1 / FVC < 0.70$ confirms the presence of persistent airflow limitation (GOLD, 2014). Elbehairy et al., recommend screening by spirometry in smokers at risk (Elbehairy, Webb, Neder, & O'Donnell, 2013). Other strategies may be considered as part of the diagnosis and assessment of COPD which includes: chest radiographs, lung volumes and diffusing capacity, oximetry and ABG analysis, alpha-1 antitrypsin deficiency screening, exercise testing, and composite scores (GOLD, 2014).

There are four integral components for COPD assessment: symptoms, degree of air flow limitation, risk of exacerbations, and comorbidities (GOLD, 2014). GOLD created a rubric for

combining these assessments to improve COPD management (GOLD, 2014). The degree of airflow limitation is classified based on post- bronchodilator FEV_1 . Patients with COPD are classified into four grades: GOLD 1 has a mild airflow obstruction with $FEV_1 \geq 80\%$ of predicted; GOLD 2 has a moderate airflow obstruction with FEV_1 50–80% of predicted; GOLD 3 has a severe airflow obstruction with FEV_1 30–50% of predicted; and GOLD 4 has a very severe airflow obstruction with $FEV_1 < 30\%$ of predicted. This definition provides an objective method to classify the severity of airflow limitation in COPD (GOLD, 2014).

Treatment and Management

Unfortunately, about 60-85% of COPD patients, especially in its mild to moderate stages, remain undiagnosed (Decramer et al., 2012). Both pharmacological and non-pharmacological management strategies are crucial in the management of COPD exacerbations. Pharmacologic therapy is used to reduce symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance (GOLD, 2014). Non-pharmacological strategies improve health status and quality of life, reduce healthcare utilization, and costs by preventing the frequency and severity of COPD exacerbations (Suh, Mandal, & Hart, 2013).

Smoking cessation is the most important factor that influences the natural history of COPD (GOLD, 2014). Non-pharmacological management strategies include the following: pulmonary rehabilitation, non-invasive ventilation, smoking cessation, long-term oxygen therapy, tele-health programs, and physiological monitoring (Suh, Mandal, & Hart, 2013). Furthermore, physical activity is beneficial for COPD patients; and they should repeatedly be encouraged to remain active (GOLD, 2014).

Prevalence and Incidence Rates

Worldwide: The prevalence and mortality rates of COPD are increasing worldwide; and therefore remains a relevant public health problem. In 2008, the WHO predicted COPD to be the third leading cause of death by 2030 globally. COPD affected approximately 329 million people (4.8% of the global population) in 2010, which is much higher than the earlier figure of 64 million in 2004 (Vos et al., 2012).

Canada: Although COPD is a preventable and treatable condition; it is the fourth leading cause of death in Canada (Statistics Canada, 2011). In 2009, approximately 4.2% of the population (aged 35 and over) reported that they had been diagnosed with COPD. This rate did not change significantly from 4.6% in 2008, and there was no significant difference between the sexes (Statistics Canada, 2011). Direct measurements of lung function from the Canadian Health Measures Survey ([CHMS], 2013) indicated that 13% of Canadians had a lung function score indicative of COPD, which is three times higher than the reported rate (Statistics Canada, 2013). This disparity between reported and measured COPD in the CHMS suggests under diagnosis of the disease in Canada (Evans et al., 2014).

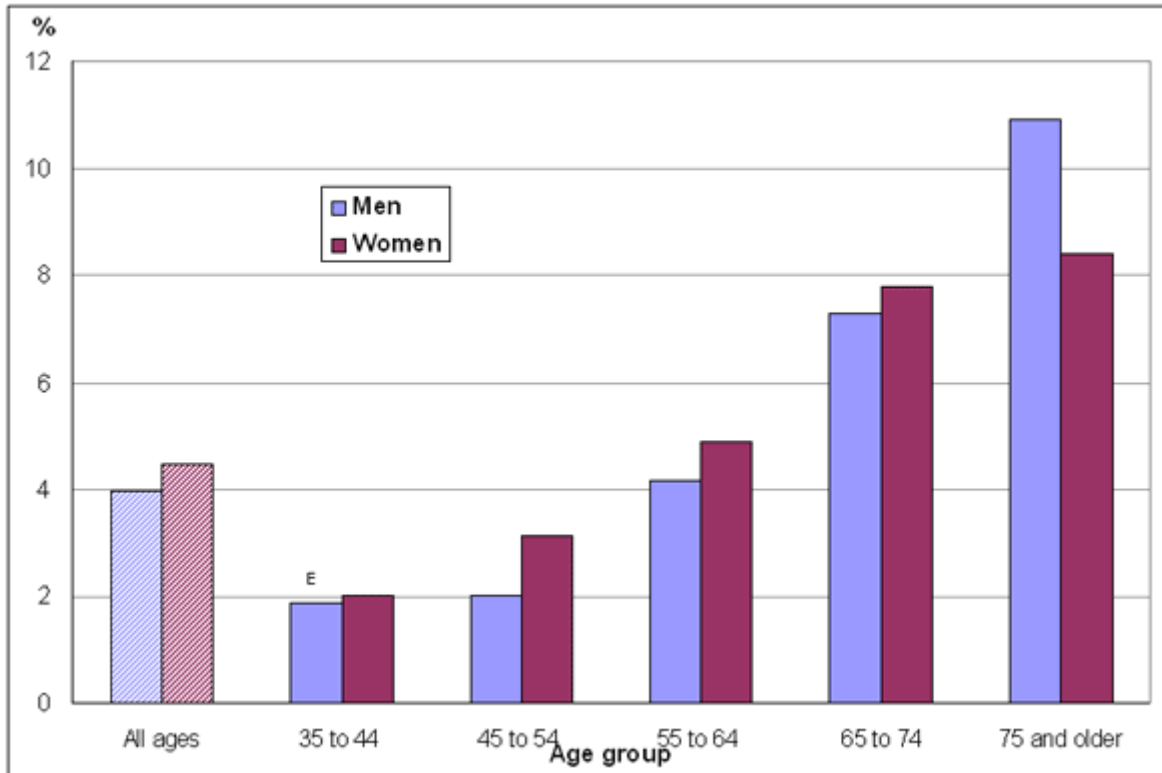


Figure 1.2: **Prevalence of physician-diagnosed COPD by age and sex in Canada, 2009**

In 2013, the Alberta, Saskatchewan, and Newfoundland population aged 35 and over, who reported being diagnosed by a health professional with chronic bronchitis, emphysema or COPD was reported at 4.1%, 3.2%, and 4.9% respectively (Statistics Canada, CCHS, 2013).

Figure 1.2 shows how COPD prevalence changes as the population ages. Among men, COPD rates increased steadily from age 35 and remained high; on the other hand, women's COPD rates increased from age 35 but leveled off at age 65 (Statistics Canada, 2011).

Epidemiological challenges

Estimates of the prevalence and incidence of COPD are very dependent upon the definition of COPD. This limits the comparability of the prevalence and incidence between studies. There are various risk factors that led to the increased prevalence of COPD. Its primary cause is tobacco smoke, including second-hand or passive exposure. Another risk factor is

exposure to air pollution, such as in the use of biomass fuels. Occupational exposure to dusts causes SOB, thus avoiding dust may reduce COPD exacerbations (Rehm et al., 2007). Also, genetic causes may also play a role in increasing the risk of COPD. This includes the deficiency of alpha-1-antitrypsin, an anti-protease which protects the lung tissue from damage, and predisposes patients to COPD (Rehm et al., 2007).

Economic burden

An acute exacerbation of COPD has detrimental effects on lung function, health-related quality of life (HRQL), and exercise capacity (Suh, Mandal, & Hart, 2013). COPD imposes a significant economic burden on healthcare systems. The Conference Board of Canada stated that the combined direct and indirect costs of COPD would increase from just under \$4 billion in 2010 to about 9.5 billion by 2030, an increase of 140 per cent (Thériault, et al., 2012). In 2010, the three major chronic lung diseases, costing Canada's economy \$12 billion, were asthma, COPD, and lung cancer; with the annual economic burden predicted to double by 2030 if strategies to manage respiratory disease are not developed (the Conference Board of Canada, 2012).

In 2011, Statistic Canada conducted a "Survey on Living with Chronic Diseases in Canada (SLCDC)". The survey included a nationally representative sample of 1,133 Canadians aged 35 years and older who reported being diagnosed with COPD by a health professional. They stated that COPD is devastating in nature and negatively impacts an individual's quality of life. Among Canadians with COPD, 45% reported their overall health as "fair or poor" (PHAC, 2012). COPD affected their activities of daily living and occupational status by reducing the number of hours worked or changing the type of work. As COPD progresses, it limits the quality of life and activity levels due to SOB (Rehm et al., 2007). According to the Canadian Institute

for Health Information [(CIHI), 2008], COPD now accounts for the highest rate of hospital admission among major chronic illnesses in Canada. In addition, it has a much higher readmission rate than other chronic illnesses.

Respiratory diseases pose a significant economic burden on the Canadian health care system due to both direct and indirect costs. Currently, almost 6.5% of total health care costs were related to respiratory diseases (not including lung cancer) (PHAC, 2007). The direct costs result from outpatient and inpatient care expenses; alternatively, the indirect costs arise due to the loss of productivity. Mittman et al., estimated the total cost of COPD hospitalization in Canada to be \$1.5 billion a year (Mittman et al., 2008).

Mortality

COPD is preventable as the majority of cases are caused by smoking. Smoking is accountable for approximately 80% of deaths from COPD (Rehm et al., 2007). Quitting smoking has been associated with improved lung function, reduced chronic cough and airway mucus production, and decreased mortality from COPD (PHAC, 2012). In China, with one-third of the world's smokers, the current predictions of the annual COPD mortality rate will be over 2 million by 2033 (Lin, Murray, Cohen, Colijn, & Ezzati, 2008).

1.2.2.3 Cardiopulmonary diseases associated with Shortness of Breath

In addition to obstructive diseases, SOB can be an underlying symptom for restrictive lung diseases. Restrictive diseases affect the volume of the lungs more than actual airway flow. The expansion of the lung is restricted which reduces lung capacity, either due to loss of alveolar volume, or diseases of the chest wall, pleura or neuromuscular impairment. Thus, the lungs of patients with restrictive airway disease will occupy less volume than the lungs of healthy individuals.

Heart Failure (HF) is a physiological state that occurs when the heart cannot pump enough blood to meet the metabolic needs of the body. There are many risk factors that increase incidence of HF with poor predicted outcomes such as ischemic heart disease, hypertension, smoking, obesity, and diabetes (Bui, Horwich, & Fonarow, 2010). HF is a major public health issue and it afflicts 23 million people across the globe (Lloyd-Jones et al., 2010; McMurray, Petrie, Murdoch, & Davie, 1998). More than 550,000 individuals are diagnosed with HF every year in Canada; in addition, there is a lifetime risk of one in five to develop this syndrome (Lloyd-Jones et al., 2010; Levy et al., 2002). Depending on the severity of symptoms, heart dysfunction, age, and other factors, HF can be linked with an annual mortality rate between 5% and 50% (Arnold et al., Canadian Cardiovascular Society [CCS], 2006).

Pulmonary arterial hypertension (PAH) is a rare chronic disease that affects both the heart and lungs. It occurs due to proliferation of smooth muscles and vascular endothelium of pulmonary arteries. It leads to impaired diffusion and decreased supply of the oxygenated blood. As a result, patients with PAH suffer from SOB, fatigue, and eventually it leads to right HF (National Heart, Lung, and Blood Institute [NHLBI], 2014). As a result, patients with PAH suffer from SOB, fatigue, and eventually it leads to right HF (NHLBI, 2014). Peacock and colleagues suggested that previous reports, from specialist centres of pulmonary arterial hypertension management, underestimated the true incidence and prevalence of PAH; furthermore, they stated that no studies have examined the epidemiology of PAH beyond the experiences and records of specialist centres and national registries (Peacock et al., 2007).

1.3 Care gaps exist in diagnosis, treatment and management of SOB patients

Many diseases have SOB as a common symptom that causes a wide spectrum of challenges for family physicians (FPs). Therefore care gaps may exist in terms of diagnosis, treatment, management, and prognosis for the specific disease underlying this condition. Community patients with onset of asthma and COPD are often poorly managed. Spirometry, the primary component of pulmonary function tests (PFTs), and full PFTs are required to diagnose the two most common types of obstructive airways diseases - asthma (reversible) and COPD (non-reversible). These evaluations however, are not often performed.

Most patients with SOB are prescribed pharmacological therapy without a full diagnostic workup for the cause of the symptoms. Therefore innovative research programs that are designed to assess patients' outcomes and management are needed to elucidate where the care gaps exist.

1.4 Community pharmacy assisted interventions

Recently, changes in the scope of practice across Canada enhanced the participation of pharmacists with other healthcare professionals to provide primary healthcare and chronic disease management. Pharmacists are accessible and are often the first point of entry into the health care system (Tsuyuki et al., 2002). They are present in almost every community, and see patients more frequently than physicians. Dr. Ross Tsuyuki's research group in Edmonton has pioneered the development of networks of community pharmacists as a public health approach to chronic disease management. As an example, his study of Cardiovascular Risk Intervention by Pharmacists (SCRIP) recruited 675 patients in 54 centres; the study was a randomized trial of a community pharmacist intervention versus usual care in patients at high risk for cardiovascular events (Tsuyuki et al. 2002). Patients were identified by the community pharmacists through medication indicators, such as use of nitroglycerin or oral hypoglycemic agents. In the SCRIP

study, patients received a multifaceted intervention aimed at improving cholesterol risk management. Dr. Tsuyuki's research group successfully extended a pharmacy management model to include improving care in asthma, osteoporosis, osteoarthritis, hypertension, and diabetes.

In this thesis, we are interested in assessing how a community pharmacy may help in the screening patients suspected to have OADs by using the PiKo-6 portable spirometer. At the time of the study initiation, there was no study conducted to assess the use of the PiKo-6 in community pharmacies to screen patients for OADs. The PiKo-6 could be the first diagnostic step to target patients with SOB symptoms for a more complete evaluation of airway diseases.

Chapter 2: Pulmonary Function Testing

2.1 Spirometry - the primary diagnostic tool for airway disease

Pulmonary function testing (PFT) is the main diagnostic tool for quantifying respiratory effort and detecting airway obstruction. Spirometry, the measurement of airflow, is the most useful component of PFT to detect airway obstruction. Spirometry is the most reproducible and objective measurement of airflow limitation available (GOLD, 2014). Qaseem et al., recommends spirometry for patients with SOB (Qaseem et al., 2011). Spirometry measures lung function by quantifying the amount (volume) and /or speed (flow) of air that can be inhaled and exhaled in forced breathing. In a laboratory, PFT is performed using a device called a spirometer, which comes in several different varieties such as the HDpft 3000™, SpiroAir™ and Body Plethysmograph™. Most spirometers display the rate of airflow and the total volume of air inspired or expired in graphs called spirograms. PFT varies slightly depending on the settings, the equipment used, and the patient's current effort at discharging air out of the lungs (Mason et al., 2010).

Generally, patients performing spirometry are asked to take the deepest breath possible, and then exhale into the sensor as hard as possible for the longest possible time at best effort to discharge the total volume of air in the lungs. This procedure may be directly followed by a rapid inhalation (inspiration), especially when evaluating possible upper airway obstruction. During the test, a soft nose clip is used to prevent air from escaping through the nose. Filtered mouthpieces are also used to prevent the spread of microorganisms. In family practice, the volume of air discharged during breathing and flow rates that are of interest to patient care are recorded as: Forced Expiratory Volume in 1 second (FEV₁), Forced Vital Capacity (FVC), Peak

Expiratory Flow (PEF), Ratio of FEV_1/FVC , and Forced Expiratory Time (FET) (Coates et al., 2013).

Smokers, especially those likely to develop COPD, experience an increased rate of decline in FEV_1 (Vestbo et al., 2011). FVC is the total volume of exhaled air from the deepest inspiration to total exhalation. The FEV_1/FVC ratio, which represents the % of air that can be expelled in the first second, defines COPD and also provides insight to its severity. Experienced pulmonologists will use flow-volume loops, with the graphical display of the relationships between the flow rates and volumes during a forced exhalation, to diagnose patients with the presence of airway obstruction. Family physicians (FP) or clinicians, who are less familiar with PFT diagnosis, may find that numerical data of FEV_1 and the FEV_1/FVC ratio are more useful. PEF, the maximum flow rate achieved during the forced exhalation, can be obtained using an inexpensive portable handheld peak flow meter for domestic use. Although the PEF is not a diagnostic tool, it can be used for practical monitoring to help patients and clinicians monitor the course of asthma and to detect early increase in airway obstruction (GINA, 2014). FEV_1 from spirometry is more reliable than PEF; as a result, it is recommended to replace PEF with FEV_1 (GINA, 2014).

In PFT, the addition of beta-agonist inhalation to standard spirometry allows assessment of reversible airway obstruction. First, a baseline spirometry is performed followed by administration of an inhaled bronchodilator, either by meter-dose inhaler or by a nebulizer. After 15 minutes, the spirometry is repeated. An improvement in FEV_1 of 12-15 % from the baseline is considered a positive response, which supports a diagnosis of reversible airway obstructive disease (GINA, 2014). In the absence of an acute viral infection, a 12-15 % improvement from the baseline in FEV_1 is also sufficient evidence for a diagnosis of asthma.

Patients with suspected airway obstruction may not show airflow limitations at the time of initial assessment. As a result, they may be referred to perform a bronchial provocation test to assess airway hyperresponsiveness (GINA, 2014). The bronchial provocation test uses a variety of potentially broncho-provocative stimuli, including allergens, methacholine, histamine, exercise, and/ or cold air. This bronchial provocation test applies to patients suspected with asthma rather than COPD. It allows for diagnosis of reversible airway obstruction, especially in more borderline or asymptomatic patients who are suspected to have asthma but have no history of SOB symptoms, coughing or wheezing.

The American Thoracic Society (ATS) developed standard guidelines for the performance and interpretation of PFT. These guidelines are reviewed, revised, and updated each year. When interpreting spirometry results, it is essential to evaluate airway obstruction, acknowledge the patients' baseline history, physical evaluation, and clinical symptoms. Figure 2.1 presents the diagnostic algorithm for obstructive airway diseases in patients with SOB.

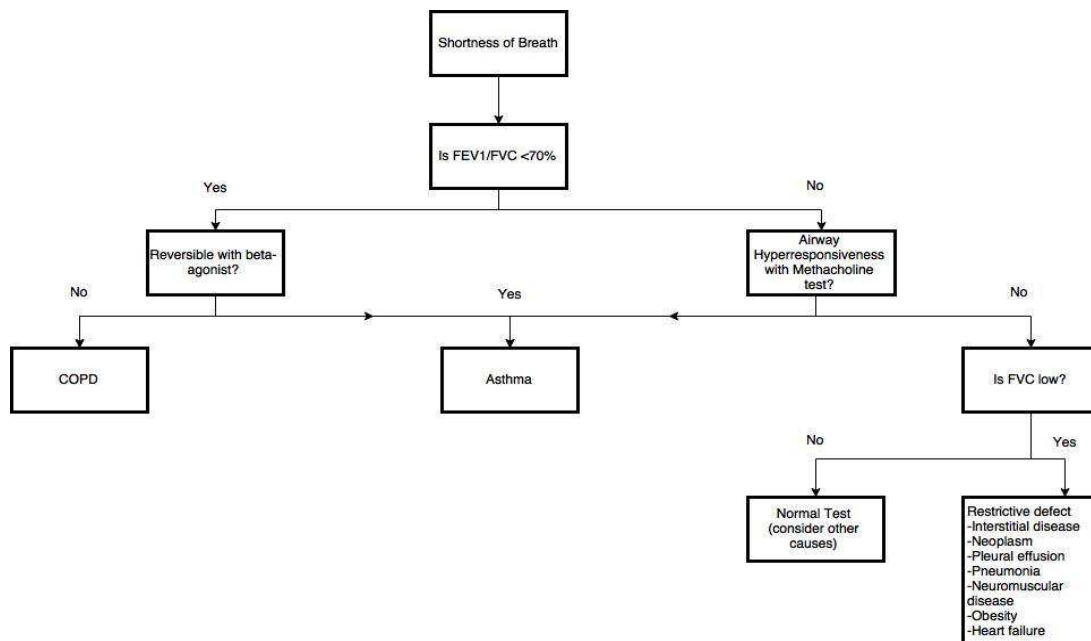


Figure 2.1 **Diagnostic algorithm for shortness of breath** (modified from Hueston, 2002).

In spirometry testing, a ratio of FEV₁/FVC that is lower than 70% is a diagnosis of airway obstruction (GOLD, 2014). If the obstruction is reversible with inhalation of a beta-agonist, asthma is the most likely diagnosis. Patients with COPD may have reversibility, but it is usually minor. If the reversibility element is large in a patient with obvious COPD, distinguishing asthma from COPD can be problematic, particularly in smokers and older adults. The consensus-based description of patients with Asthma and COPD Overlap Syndrome (ACOS) is currently available in the GINA and GOLD reports (GINA, 2014; GOLD, 2014). Alternatively, a low FVC accompanied with normal FEV₁/FVC suggests a restrictive defect. These patients may be carefully evaluated using other diagnostic modalities to determine the underlying cause of the disease, which may include a variety of diseases.

Several patient and laboratory factors, other than the underlying disease, may affect PFT or spirometry variability in determining airway obstruction. Factors such as age, gender, height, and ethnicity are considered in calibration of the spirometer test results. Many laboratory spirometers calculate both the actual test value and the predicted value. The predicted value adjusts for age, gender, height, and ethnicity when reporting a patient's performance against the normal values.

2.2 The need for portable spirometry in family care practice

Although adult patients with SOB symptoms require spirometry to obtain a diagnosis for their airway diseases, only a few FPs perform these tests to provide optimal care for their patients. In a study that reviewed 3072 patients in an asthma research group in Alberta, only 25% of patients in family practices had PFTs performed (Tsuyuki et al., 2005). In addition, Gershon et al., stated that only about one third of individuals who had been given a diagnosis of COPD in Ontario, Canada, received PFT to confirm their diagnosis of COPD (Gershon et al., 2014). Aaron

et al., found that one-third of Canadians with physician-diagnosed asthma did not have asthma when objectively assessed with a PFT (Aaron et al., 2008). When PFTs are not often performed, patients are often misdiagnosed or received sub-optimal care (Walters et al., 2011). Aside from diagnosis, it is recommended to perform spirometry at least once a year to identify patients whose lung function is declining quickly (GOLD, 2014). Patients with COPD, who are current smokers, exhibit an accelerated decline in FEV₁ (Vestbo et al., 2011). This decline could be detectable by frequent spirometry in family care practice for early management of the disease.

Several documents sponsored by international organizations in respiratory medicine, such as the Canadian Thoracic Society (CTS), the American Thoracic Society (ATS), and the European Respiratory Society (ERS), the Global Initiative for Asthma (GINA), and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) have indicated that spirometry is necessary for the diagnosis of OADs (Coates, 2013; Qaseem et al., 2011; GINA, 2014; GOLD, 2014). The ATS/ERS (2005) standards advocate performing spirometry in all individuals with a history of exposure to cigarette smoke and/or environmental pollutants, a family history of COPD, or the presence of a chronic cough, sputum production, or SOB (Miller et al., 2005). Despite recommendations by these national and international bodies, FPs have been slow to adopt routine spirometry diagnosis in their clinical practice for patients with symptoms of SOB. Usually, inhalers are prescribed to relieve symptoms without diagnostic workup.

Little is understood about factors that limit spirometry use in family clinical practice. In the Canadian health care system, spirometry is almost always performed in pulmonary function laboratories, but not in general medicine clinics or family practice, a situation that may differ from that in many other health-care systems. There are several factors that may be related to the lower rates of use of spirometry in family practice in Canada. Gershon et al., stated that some of

the factors that influence the use of spirometry were age, comorbidity, and age of the family physician (Gershon et al., 2014). Patients with older primary care physicians were less likely to receive testing (Gershon et al., 2014). Furthermore, another study in Montreal, Canada, stated that the lack of allocated time and training for health care professional makes the implementation of spirometry challenging (Saad et al., 2014).

Early detection, accurate diagnosis, optimal evaluation, and management of airway obstruction are considered to be the responsibility of the primary care physician (Spyratos et al., 2012; Saad et al, 2014). Usually, FPs are faced with the dilemma of carefully selecting patients for PFT in order to balance the cost and inconvenience of testing with the likely benefits. Nevertheless, the current GOLD and GINA guidelines require spirometry to diagnose both COPD and Asthma (GOLD, 2014; GINA, 2014). In addition, health care professionals performing spirometry require training to perform PFT and interpret the results, to avoid missed diagnosis and enhance management of the disease (Levy et al., 2009). CTS offers training courses on how to conduct quality spirometry testing that includes knowledge of spirometers, understanding of the ATS/ERS standards for spirometry, quality control, patient instruction and basic interpretation of the results (Coates et al., 2013). The lack of spirometers in primary health care facilities could impair primary health care physicians from providing adequate care to patients with OADs.

COPD has been defined by the GOLD as an irreversible condition, which is diagnosed by fixed cut-off points of FEV_1/FVC ratios. The FEV_1/FVC ratio often requires a prolonged exhalation time for up to 12 seconds to achieve complete lung emptying. Unfortunately, many elderly subjects or patients with severe respiratory diseases cannot make such vigorous physical effort (Bellia et al., 2008). Lee et al., stated that that elderly are less likely to undergo pulmonary

function testing (Lee, Bartle, & Weiss, 2006). Alternatively, Gershon et al. stated that younger age might have been associated with a lower likelihood of testing because physicians did not suspect their younger patients had COPD (Gershon et al., 2014).

The recent GOLD guidelines have recommended that spirometry should be performed in a follow-up assessment 4 to 6 weeks after discharge from the hospital to monitor changes in spirometric parameters (GOLD, 2014). As a response to this recommendation, performing spirometry using a portable spirometer in family practice may improve management for patients with obstructive airway diseases. Using a portable spirometer could facilitate early recognition of exacerbations and timely detection of treatment failure during an exacerbation.

2.3 Reasons for lack of spirometry testing in pharmacy practice

There are many factors associated with the lack of spirometry testing in community pharmacies. Cawley, Pacitti, & Warning stated that some pharmacists feel that spirometry is outside their scope of practice (Cawley, Pacitti, & Warning, 2011). The role of pharmacists in screening patients suspicious of having OADs should be acknowledged among pharmacists and other health care professionals. Pharmacists might be able to screen patients suspicious of having OADs using the micro-spirometer (Piko-6), then report patients with limited airflow to their primary health care physician for a complete assessment of the disease, if it was lacking. Currently, respiratory therapists are the main medical professionals responsible for pulmonary function testing in the hospital environment. Unfortunately, respiratory therapists are limited in their scope of practice to the pulmonary patient and many primary health care facilities lack the services of a respiratory therapist (Cawley, Pacitti, & Warning, 2011).

The limited training provided to pharmacists, to perform spirometry, is another reason for lack of testing (Cawley, Pacitti, & Warning, 2011). In Memorial University of Newfoundland

and Labrador, pharmacy students are taught the basics of spirometry procedure and interpretation. However, the training provided is not sufficient to perform spirometry in community pharmacies. Students were not instructed to perform spirometry in the pharmacy due to the lack of studies that validated the use of spirometry in community pharmacy settings. Furthermore, most community pharmacies are not equipped with spirometers. Fuller et al., stated that many patients were motivated to participate in spirometry testing because the screening was free. However, it was unclear if patients would have participated if a cost had been associated with the screening (Fuller et al., 2012). In addition, in the current health-care environment, pharmacists trained in spirometry testing would most likely want to receive financial compensation (Cawley, Pacitti, & Warning, 2011).

2.4 The need for portable spirometry to detect airway obstruction

In 2000, a consensus statement from the National Lung Health Education (NLHEP) program recommended the development of portable spirometers that can be specifically used for family care or office practice (Ferguson et al., 2000). The NLHEP developed a compliance checklist for office spirometers based on the ATS/ERS (2005) guidelines (NLHEP, 2012). The CTS recommends the use of the NLHEP guidelines when choosing an office spirometer (Coates et al., 2013). It was expected that the new categories of these machines may lessen the burden and difficulty of using the sophisticated and complicated spirometers that are used in hospitals and PFT laboratories, where formal testing usually takes place. Since most FPs in office practices do not need the level of sophistication present in these more expensive machines, portable office-based spirometers may make spirometry more accessible and affordable for patients in the ambulatory setting. Currently, many lung air flow –sensing devices have been developed to measure the flow rate of exhaled air and integrate these data with the time of

exhalation to provide an automated printout of preselected volumes and flow rates such as the Vitalograph In2itive™ and Nspire KoKo pft™. These devices are gaining popularity in research for screening obstructive airway diseases and office practice due to their small size, ease of use, low cost. In addition, some portable spirometers are combatable with disposable mouth piece to prevent the patient from inhaling potentially contaminated air through the spirometer.

2.4.1 The PiKo-6 portable spirometer

The PiKo-6 micro-spirometer is a one of the recent digital handheld spirometers designed to quickly perform lung function testing for patients with shortness of breath, coughing, or wheezing. The piKo-6 met the American Thoracic Society (ATS) recommendations on intra-device precision of monitoring devices and it has been approved for use by Health Canada. The PiKo-6 measures the following lung volume measures:

pFEV₁: Piko-6 measure of forced expiratory volume in one second

pFEV₆: Piko-6 measure of forced expiratory volume in in six seconds

pRatio: the ratio of pFEV₁/pFEV₆

Patients using the PiKo-6 device are required to fill their lungs with air and blow it out as hard as they can. The maneuvers recommended for the use of the device are outlined in Table 2.1.



Disposable Patient Mouthpiece



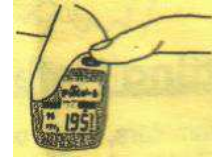
PiKo-6 Rubber Mouthpiece Adapter



The PiKo-6 machine

Table 2.1 *Maneuvers for Performing the PiKo-6 Test (Steps are adapted from the device manual for commercial purpose)*

NOTE: Before you start, mount the disposable mouthpiece to the PiKo-6 device. When the LCD display is blank, press the “Operate” button once and the PiKo-6 will turn on. Ignore numbers that may appear on the screen.



STEP 1: Stand up straight with your head straight up to open your airways. Do not sit down or bend your head down while performing the test. Hold the PiKo-6 horizontally in your right hand and the LCD display pointing up. **DO NOT COVER THE VENT HOLES**



STEP 2: Bring the PiKo-6 up close to your face and press the operate button momentarily with your index finger. A short beep will be heard.



STEP 3: Inhale as much air as you can to fill your lung when the second beep is heard and the “blow animation” appears.



After the second beep, you have 10 second to start blowing.
If the “blow animation” disappears you have to repeat STEPS 1 to 3.



STEP 4: Place the mouthpiece in your mouth and blow as hard as you can for at least 6 seconds until an “end of blow” beep sounds. Keep the PiKo-6 horizontal.



Test Results: Your lung test values for FEV₁, FEV₆ and FEV₁/FEV₆ will automatically start to display sequentially on the LCD.

IMPORTANT: If a cough has been detected while you were blowing, or your effort was too short, or you had a slow start, a “!” symbol may appear next to your FEV₁, FEV₆, and FEV₁/FEV₆ values.

This means you need to repeat STEP 1 to STEP 4 until you get a correct result.

The PiKo-6 stores and displays the test results; therefore, it may be a useful device to self-monitor development of COPD and asthma conditions. Recent studies have evaluated the screening utility of the PiKo-6 device and assessed the reliability of the PiKo-6 spirometer by comparing it with laboratory spirometers (Bemt et al., 2014; Frith et al. 2011; Wada et al., 2010; & Kaufmann et al., 2009). These studies were critically appraised and included in chapter 5 (Discussion and Conclusion).

2.5 FEV₁/FEV₆ replace FEV₁/FVC ratio to detect airway obstruction

Forced Expiratory Volume in 6 seconds (FEV₆) has been shown to be a good surrogate marker for forced vital capacity (FVC). An exhalation in six seconds is easier to accomplish in most patients than obtaining the full FVC in laboratory setting. Many studies recommend replacing the FVC used in PFT spirometers with FEV₆ (Nwagha et al., 2014; Perez-Padilla et al., 2013; & Jing et al., 2009). These changes have been necessitated to minimize the measurement error in FVC. The measurement error frequently occurs as a result of failed attempts at full exhalation between 6 and 10 seconds of maximum patient effort, especially in elderly patients. Establishing FEV₆ as the standard parameter would eliminate this uncertainty. Instead of the FEV₁/FVC ratio, the new FEV₁/FEV₆ ratio has been proposed and validated as a parameter for screening and assessing obstructive airway diseases (Jing et al., 2009; Nwagha et al., 2014). Jing et al., systematically and quantitatively evaluated published studies that assessed FEV₁/FEV₆ ratio, as a valid alternative to the FEV₁/FVC ratio (Jing et al., 2009). Here, they reported that a reliable FVC measurement was obtained in less than 60% of spirometric measurements. Alternatively, another study reported that a reliable FEV₆ measurement was obtained in more than 80% of spirometric measurements (Bellia et al., 2008; Glindmeyer et al., 1987). Furthermore, Perez-Padilla et al., stated that the FEV₁/FEV₆ ratio is a more reliable index than

the FEV₁/FVC ratio, as FVC varies within the duration of the forced exhalation (Perez-Padilla et al., 2013). The FEV₆ measurement creates less discomfort for the patients than FVC, especially in elderly subjects or patients with severe respiratory diseases (Jing et al., 2009). As a result, FEV₆ measurements may be easier to perform than full exhalations (FVC). The NLHEP checklist for office spirometers compliance with NLHEP guidelines accepts FEV₆ as an alternative for FVC (NLHEP, 2012). Although FEV₆ has been validated in many studies, the various respiratory groups (GINA, GOLD, CTS, and ATS) have not yet released position statements on it. Therefore FEV₁/FEV₆ assessment in primary care with a micro-spirometer, such as the PiKo-6 portable device, may be useful in the baseline diagnostic work up of patients who are suspected of having an OAD. In this context, assessment of the utility of portable spirometry for screening in community patients in the pharmacy settings could lead to significant benefits, such as improving the appropriateness of diagnostic test prescription and facilitating the early diagnosis of asthma and COPD.

2.6 The PiKo-6 study proposal

The current study hypothesized that the PiKo-6, when delivered by community pharmacists to patients suspected to have OADs, correlates well with the results from standard laboratory spirometry.

2.6.1 Research question

In patients with inhaler prescription for the relief of shortness of breath with an unknown cause, do the PiKo-6 measures of lung function correlate well with the standard Pulmonary Function Test measures of lung function?

Population of interest: patients with inhaler prescription for the relief of airflow limitation with an unknown cause

Intervention: Trained pharmacist used the PiKo-6 to measure pFEV₁, pFEV₆ and the pRatio

Comparison: Laboratory specialists used the standard spirometer to measure FEV₁, FVC and FEV₁/FVC

Objective: Correlation and validity of the Piko-6 portable spirometer compared to the laboratory spirometer.

2.6.2 Research objectives

1. To analyze the repeatability of the PiKo-6 spirometry applied at 5-minute interval in community pharmacy settings;
2. To measure the accuracy of the Piko-6 lung volume measures (pFEV₁, pFEV₆ and the pRatio) by comparing it with the laboratory spirometry lung volume measures (FEV₁, FVC and the ratio);
3. To analyze the screening utility of the PiKo-6 spirometry by comparing physician-diagnosed COPD (using the laboratory spirometer) at various cut-off values of the Pre-Bronchodilator pRatio (pFEV₁, pFEV₆) for maximal sensitivity, specificity, positive predicted value (PPV), negative predicted values (NPV), and the area under Receiver Operating Characteristic (ROC) Curves.
4. To evaluate whether bronchodilator administration modifies the concordance observed in standard laboratory spirometry data ratio with the pRatio obtained from the PiKo-6.

Chapter 3: Methods and Materials

3.1 Overview and study design

The current study is a sub-study of a large research program titled “The Investigation of the Epidemiology of Shortness of Breath (EpiSOB) –A Public Health Approach” (Midodzi et al., 2010). The current thesis analyzed the data collected from the EpiSOB study. The large EpiSOB study was conducted in Edmonton and Saskatoon between November 2008 and May 2013. To summarize, the EpiSOB research program seeks to identify existing care gaps in diagnosis, treatment, and management of patients with SOB symptoms. The EpiSOB study was conducted at the Epidemiology Coordinating and Research (EPICORE) center at the University of Alberta, Edmonton, Canada. The EpiSOB program study design, the data collection instruments and methods have been described in detail elsewhere (Midodzi et al., 2010). Figure 3.1 presents the flowchart of the EpiSOB program overview.

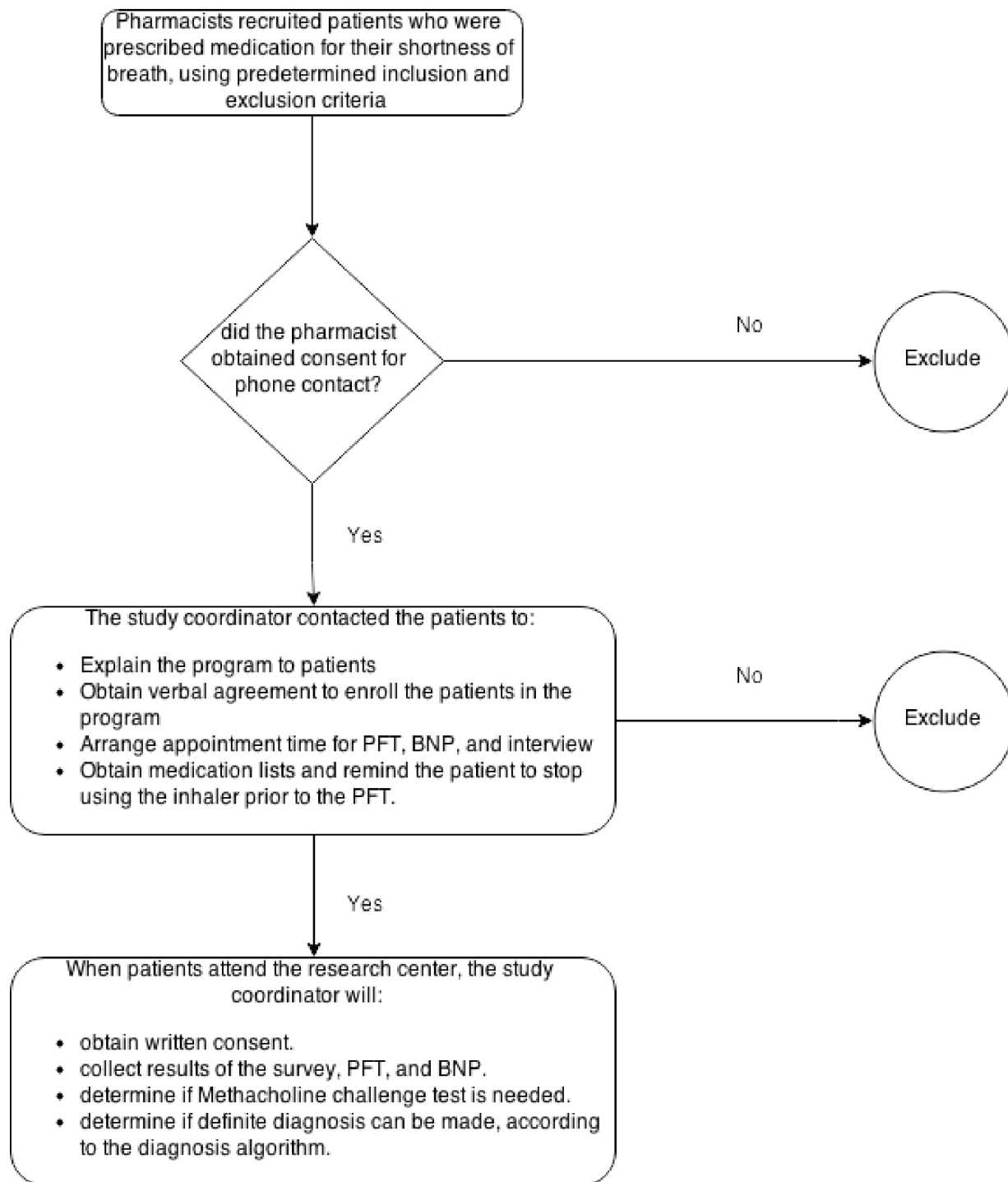


Figure 3.1 **Epidemiology of Shortness of Breath program overview**

Figure adapted from (Midodzi et al., 2010).

3.2 Community pharmacy recruitment and training

Randomly selected pharmacies (n=25) in Edmonton and Saskatoon, Canada, were invited to participate in the study. Standard letters of invitation were sent to the managers of all selected pharmacies. The letters explained the study objective, procedure, and outcomes. Of these, 12 pharmacies responded and were enrolled for patient recruitment. At each pharmacy, a designated pharmacist was responsible for patient recruitment. The recruiting pharmacists were invited to the study center at EPICORE for two hours of training sessions. Trained physicians and study coordinators performed the training sessions. The sessions clarified the process of recruiting subjects, explaining study protocol, completing the study forms, performing the PiKo-6 spirometry, and assessing the patient's current medication use.

3.3 Patient recruitment and data collection

3.3.1. Recruitment

Recruited patients were 18 years or older with an active prescription (dispensed within the past 6 months) for a Short-Acting Beta-Agonists (SABA), Short-Acting Anticholinergics (SAAC), Long-Acting Beta-Agonists (LABA), and/or Long-Acting Anticholinergics (LAAC), including combination products and inhaled steroids by a family physician. Patients who cannot communicate in English (unless a family member or friend can accompany the patient to the visit and interpret); who are unwilling or unable to come in for pulmonary function testing and a physical examination, were pregnant females or do not provide informed consent were excluded.

Pharmacists used two methods to recruit patients. First, pharmacists identified patients attending pharmacies with new prescription or when obtaining refills for their asthma or COPD

medication. The second method was done via screening the pharmacy records for patients with a new prescriptions or refills for their asthma or COPD medication within the past 6 months. As part of the informed consent process, pharmacists obtained verbal consent to obtain spirometry tests using the PiKo-6 spirometer. In addition, pharmacists asked the patients for permission to contact their family physician by mail or fax to enquire about the specific condition(s) for which they were prescribed medication for their airway diseases. In return, family physicians would receive the results of the study evaluations, including PFTs.

When a patient met the inclusion criteria for the program, the pharmacist used the following standard script to obtain verbal consent and allow the project office at the EPICORE Centre to contact the subjects by phone:

Hi Mr/Mrs/Ms _____ I see you are prescribed with an inhaler _____. Were you given this medication for shortness of breath?.

- *If the answer is yes:*
 - *Are you interested in finding out more about your condition? A research program conducted at the U O A and U of S is interested in patients who are given this medication for SHORTNESS OF BREATH, and to look into the cause of shortness of breath.*
- *If yes:*
 - *Can I provide your name and phone number to the Project office at the University of Saskatchewan?*
- *If patient consents:*
 - *Pharmacist Complete Patient Screening Form and fax to the research coordinating centre at the EPICORE.*

For patients that were recruited via the pharmacy data base, the pharmacist called the patients to inform them about the EpiSOB program procedures, and asked them to participate.

Pharmacists used the following standard script to recruit patients:

Hi Mr/Mrs/Ms, I noticed that you filled / refilled a prescription for _____. I am phoning to enquire if you would be interested in being part of a research program. Do you remember why you were given this medication?

- *(it needs to be SHORTNESS OF BREATH not cough).*

- *If the answer is SHORTNESS OF BREATH:*
 - *Are you interested in finding out more about your condition? A research program conducted at the U of A and U of S is interested in patients who are given this medication for SHORTNESS OF BREATH, and to look into the cause of shortness of breath.*
- *If yes:*
 - *Can I provide your name and phone number to the project office at the University of Saskatchewan?*
- *If patient consents:*

Pharmacist Complete Patient Screening Form and fax to the research coordinating centre at the EPICORE.

3.3.2. Data Collection

During the pharmacy screening, recruited patients performed two spirometry tests using the PiKo-6 spirometer. The results of the two tests were used to assess the repeatability of the PiKo-6. However, only patients attending community pharmacies, not recruited via the pharmacy records, were able to perform the PiKo-6 spirometry. The PiKo-6 test was performed according to the manufacturer's instruction. The procedure of performing the PiKo-6 spirometer is outlined in Table 2.1.

The project office at the EPICORE Centre contacted patients by phone to inform them regarding the program procedures, and asked them to participate. Consenting patients were scheduled undergo a full set of diagnostic tests including PFT, blood, and urine. The PFT test was performed according to the ATS/ERS guidelines. The process of the spirometry testing is explained by Miller et al. "Standardisation of spirometry" (Miller et al., 2005).

Blood tests included tests for heart failure biomarkers, such as Brain natriuretic peptide (BNP). When patients attended to perform their diagnostic tests, they were also asked to complete a survey to document self-reported medical history, physical symptoms, and baseline demographic information. A copy of the questionnaires and laboratory results is attached in Appendix 1. Although the EpiSOB program did not intervene at any point during the study,

diagnostic information and the findings from this program were relayed to the patient and the pharmacist.

3.3.3 Diagnosis

Three members of the EpiSOB program were physicians who specialise in respiratory diseases, including Dr. Dilini Vethanayagam, Dr. Irvin Mayers, and Dr. Brian Rowe (Midodzi et al., 2010). All three physicians were blinded to the previous diagnosis history of the patients, if they ever had a diagnosis for SOB. These physicians discussed the rationale for collecting data from physical examinations. Although it was agreed that a physical examination combined with the PFT would be the “gold standard” for diagnosis, its routine use for the purposes of the EpiSOB study would have been labour-intensive. The investigators decided to use diagnostic algorithms that were developed according to national guidelines (GINA, 2008; GOLD, 2008) and approved by the consensus of the three study physicians. The standard diagnostic algorithm for the diagnosis of asthma and COPD is presented in Figure 3.2 (Midodzi et al., 2010).

The study coordinator reviewed all test results and patient interview forms for definite diagnosis of asthma or COPD, using the diagnostic algorithms developed by the physicians. For patients with no definite diagnosis for asthma or COPD, a methacholine challenge test was arranged to determine the presence or absence of airway hyper responsiveness.

Patients whose diagnosis remained unclear after the methacholine test, had their information and test results reviewed by the three physicians for asthma or COPD adjudication. A diagnosis was upheld if there was 2/3 agreement among physician reviewers. Any patient with an unclear BNP result (100 pg. /mL) was referred to see a cardiologist consultant for further clinical evaluation. Finally, the study coordinator completed a final diagnosis form that included the final diagnosis and the method used for diagnosis (Appendix 2).

BNP is a cardiac neurohormone secreted by the cardiac ventricles in response to ventricular wall tension, pressure overload, and increased volume expansion. BNP levels have been used to follow improvement after Heart Failure therapy. A high BNP level estimates the risk of HF exacerbations (Shiber & Santana, 2006). The current Canadian Cardiovascular Society guideline to manage heart failure recommends testing of BNP levels to rule out heart failure diagnosis (McKelvie et al., 2013). Moreover, BNP testing is recommended by the Canadian Heart Failure consensus guidelines to help differentiate between shortness of breath due to lung diseases or heart failure, where BNP levels are markedly elevated (McKelvie et al., 2013). In the EpiSOB study, all patients who had BNP value greater than 100 pg./mL were referred to a cardiologist to rule out any possibility of cardiovascular cause of shortness of breath.

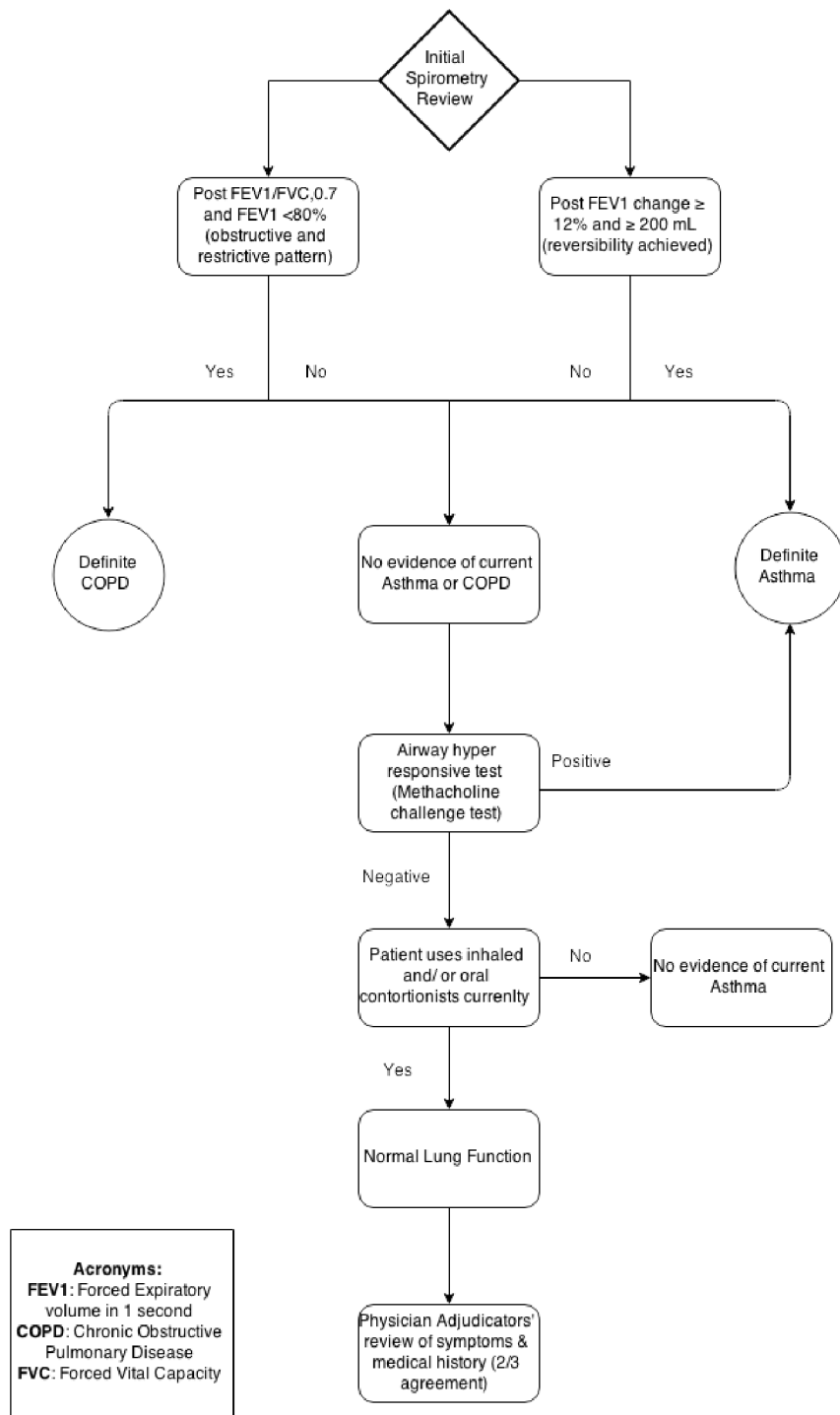


Figure 3.2 **The standard diagnostic algorithm for the diagnosis of asthma and COPD**
 Figure adapted from (Midodzi et al., 2010).

3.4 Outcome measures

To address the objectives of the current study, the analysis presented in the thesis was completed in the following five steps:

1. The demographics of subjects who volunteered or declined to perform the PiKo-6 spirometer were presented;
2. Intraclass correlation coefficient was calculated to assess the repeatability of the PiKo-6 spirometer;
3. The standard laboratory spirometer (pre and post- bronchodilator) data was presented in relation to differences across physician diagnosis;
4. The Intraclass Correlation coefficient and Bland-Altman analysis were presented to assess the validity of the PiKo-6 spirometer, obtained from the pharmacist, compared with the laboratory spirometer test, obtained by the laboratory specialist.
5. The screening utility of the PiKo-6 $pFEV_1/pFEV_6$ were assessed by examining the sensitivity, specificity, PPV, NPV at various cut-off values against the physician-diagnosis of COPD (based on standard spirometry).

3.5 Data analysis

3.5.1 Sample size calculation

The EpiSOB study was powered at 90% to determine a 70% prevalence of obstructive airway diseases (mainly asthma and COPD) in community patient with SOB. The sample size was estimated using EPI INFO v 6.04 for population surveys. Assuming that 70% prevalence of OADs in patients prescribed inhalers from family practice to relieve symptoms of SOB, a total of 323 patients will be required for a precision of $\pm 5\%$ at a confidence level of 95%. To account for

missing information, the sample size has been inflated to 350. The main EpiSob study recruited 327 patients at completion. All patients performed the standard laboratory spirometry. Of these, 234 patients were recruited in-person as the patients attend community pharmacies. Only 63 of the 234 patients volunteered to perform the PiKo-6 study.

Post-hoc justification for sample size adequacy used in the PiKo-6 analysis

a) Repeatability analysis

To assess the PiKo-6 repeatability analysis, we assess if there is a significant correlation (ρ) in measures taken at two time points (Test-1, and Test-2). Using the Fisher's Z-transformation, we assume delta (δ) is the relevant difference between the pRatio from Test1 and the pRatio from Test2. The test of hypothesis is the following: $H_0: \delta = Z \rho$ which has a standard error of $S.E(D) = \sqrt{1/(1-n)}$, where D is the estimate of ρ , Z is the fisher Z-equation, and n is the sample size required. The approximate sample size required to detect a correlation of 0.6, 0.7, 0.8, and 0.9 are 25, 17, 12 and 8 respectively (Bland, 2000, P344). The sample size would produce a 5% significant level and 90% power. Thus, there was a sufficient sample size for the result presented in the thesis under the correlational analysis (n=63). We chose to use the pRatio as a measure for the analysis because it is a composite of pFEV₁ and pFEV₆.

b) Validation analysis

In the validation analysis, we assess if the PiKo-6 spirometry measures correlate with the standard laboratory spirometry measures. In our post-hoc sample size calculation, the estimate between pRatio (pFEV₁/pFEV₆) and FEV₁/FVC was calculated. The measurements variance (VB) obtained between the PiKo-6 and the standard laboratory spirometers; and within individual patient variance (VI), obtained within the 63 patients, were: VB=0.026, and VI=0.011. Therefore, the estimate of the intraclass correlation or pulled variance between the PiKo-6 and

laboratory spirometers is 0.0262 (Bland, 2000, p.345). Assuming the maximum of the PiKo-6 pRatio from the two test was used, and assuming a 0.1 (or =10%) difference in the FEV ratio is a clinically relevant difference, the number of patients required would be approximately 55. This sample size would produce a 90% power and at 5% significance level. As a result, we can infer that our sample size of 63 subjects is adequate to assess the validity of the PiKo-6 spirometer.

3.5.2 Statistical analysis

Data was entered into the database using unique non-identifying numbers. The information was password protected. Before analysis was performed, data were cleaned, coded and entered into Statistical Package for the Social Sciences (SPSS) version 21.0 (IBM Corp., Armonk, NY) for analysis. The unclear or incomplete survey items were flagged for queries. These were brought to the attention of the research data manager where each item was discussed and a decision concerning its eligibility and entry was made.

The database was analyzed using descriptive statistics for continuous variables and frequencies for categorical variables. Univariate analysis was used to compare patients who performed or declined to perform the PiKo-6 spirometry with respect to demographics as well as prior history of comorbidities and diagnostic tests. Continuous variables were compared using the independent sample t-test while the categorical variables were assessed using a contingency table with chi-squared tests. All statistical tests were performed with an alpha significance level of 0.05.

One-way analysis of variance (one-way ANOVA) was used to evaluate the differences between the components of the pulmonary function test and their effect on asthma, COPD, or other airway diseases. The agreement and relationship between the two repeated measures using the PiKo-6 spirometer were analysed by calculating the intraclass correlation coefficient (ICC)

(2,1) and the Pearson correlation coefficient (r), respectively; the results were represented graphically using correlation graphs (Fleiss, 1986). The ICC (2, 1) test is used when each subject is measured by each rater, and raters are considered representative of a larger population of similar raters.

The variables of the $pFEV_1$, $pFEV_6$, and $pRatio$ were compared to FEV_1 , FVC, and FEV_1/FVC for each subject using a paired t-test. A high correlation does not automatically imply good agreement between PiKo-6 and lab spirometry. Bland and Altman explained that correlation alone does not show good agreement and recommended the use of Bland-Altman plots (Bland & Altman, 1986). As a result, we used reliability analysis of Bland-Altman plots to assess the agreement between the Piko-6 and standard spirometry (Bland & Altman, 1986).

When using the reliability analysis method of Bland-Altman to assess the agreement of the PiKo-6 spirometer with the standard laboratory spirometer, the patients' best expiratory flow data (i.e., highest of $pFEV_1$ and $pRatio$ values) obtained from Test 1 and 2 were used for assessing bias and limits of agreement with laboratory spirometry. According to the ATS/ ERS guidelines, the patients' best expiratory flow data is recommended to represent the patient's best effort at the time of testing (Miller et al., 2005). The Bland-Altman analysis suggest that, a clinical test instrument (in this case PiKo-6 spirometry) is valid if the deviation from the gold standard (in this case, laboratory spirometry) is not significant enough to cause problems in clinical interpretation, 95% of the values are expected to lie within $\pm 2SD$.

Bias and limits of agreement were calculated. The results were illustrated using a scatter plot. To calculate the limits of agreement, the mean difference (\bar{d}) and the standard deviation of the differences (s) were computed. Difference was calculated by subtracting the standard lab spirometry reading from the PiKo-6 reading, or from the difference between the first and second

PiKo-6 readings. The standard error = $\sqrt{3s^2/n}$, where n is the sample size (Bland & Altman, 1986). The limits of agreement = $\bar{d} - 2s$ to $\bar{d} + 2s$ (Bland & Altman, 1986). The 95% confidence interval for the bias was calculated by finding the appropriate point of the t distribution with $1 - n$ degrees of freedom; on most tables the columns marked 5% or 0.05, and then the confidence interval was from the observed value minus t standard errors to the observed value plus t standard errors (Bland & Altman, 1986).

Receiver Operating Characteristic curve analysis

Receiver operating characteristic (ROC) curves are used in medicine to determine a cut-off value for a clinical test. The ROC curves were used to determine the most suitable cut-off value for the FEV₁/FEV₆ ratio. The ROC curve analysis of the PiKo-6 spirometry test aims to find a cut-off value for the pFEV₁/pFEV₆ that will minimize the number of false positives and negatives which is the same as maximizing the sensitivity and specificity. However, it is important not to miss detecting a patient with pulmonary disease, therefore it is more important to maximize sensitivity (maximizing true diagnostic positives) than to maximize specificity (maximizing true diagnostic negatives). If the patient's test falls below the recommended cut-off value, subjects would be suspected to have an OAD. The ROC curve is a graph of sensitivity (y-axis) vs. $1 - \text{specificity}$ (x-axis). The standard laboratory (pre- bronchodilator FEV₁/FVC) and the PiKo-6 (pFEV₁/pFEV₆) were compared against physician diagnosed COPD. The physician diagnosed COPD was based on the standard laboratory spirometry (post-bronchodilator FEV₁ <80% predicted together with an FEV₁/FVC <70%).

3.6 Ethics and Confidentiality

The study protocol and consent forms were approved by the University of Alberta Health Research Ethics Board and the Biomedical Research Ethics Board at the University of Saskatchewan. Patients signed a consent form to participate in the study. In addition, the patients consented to release their medication information from the Alberta NETCARE system (www.albertanetcare.ca). Each study participant was given a study number by the pharmacy. The coordinating office received data from the pharmacies with study number and patient initials only. Any information that included patient identifier was kept at the participating pharmacies.

Chapter 4: Results

This chapter presents the study findings in three sections. The first section describes the demographics and baseline characteristics of the study sample, such as weight, co-morbidities and socio-demographics. The second section covers the repeatability of the PiKo-6, variation in repeated measurement on the same subject. In addition, the validity between the PiKo-6 spirometry data and standard laboratory testing was assessed. The last section explains the sensitivity and specificity of the PiKo-6 spirometry in relation to physician diagnosis of COPD in patients with SOB.

4.1 Baseline characteristics

A total of 475 subjects were contacted to participate in the study (Figure 4.1), of whom 241 subjects were recruited via the data base of the pharmacy and 234 subjects were recruited as they attended community pharmacies. Of the subjects who attended community pharmacies, 63 subjects performed both the PiKo-6 and the standard laboratory pulmonary function test (PFT) for spirometry to obtain physician evaluation for their final diagnosis.

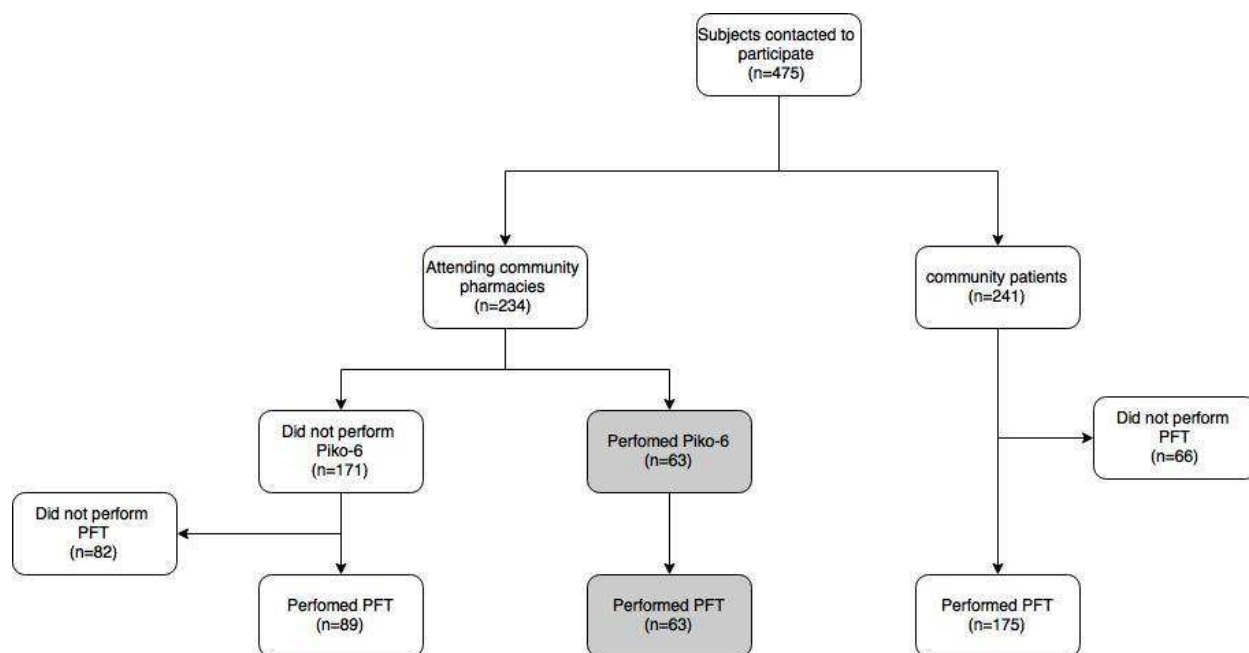


Figure 4.1 Flow chart of subject recruitment and selection.

To assess sampling bias, we investigated whether the baseline characteristics of the patients that performed PiKo-6 were similar to the patients who declined to perform the PiKo-6. Table 4.1 shows baseline and clinical characteristics of the subjects who attended community pharmacies by subjects who volunteered or declined to perform the PiKo-6 spirometry.

Table 4.1 *Assessing the differences in sample characteristics of the patients who volunteered verses those who declined to perform the PiKo-6 spirometry in community pharmacies.*

Sample characteristics	PiKo-6 Volunteer (n=63)	Declined [§] (n=89)	P-value
Age, yrs: Mean (SD)	53.9 (15.3)	54.1 (19.4)	0.936
Sex, Male: n (%)	33 (52.4)	40 (44.9)	0.366
Average BMI: Mean (SD)	31.9 (7.4)	29.4 (9.3)	0.087
Prior History of Asthma: n (%)	38 (60.3)	55 (61.7)	0.408
Prior History of COPD: n (%)	11 (17.5)	11 (12.4)	0.379
Caucasian: n (%)	47 (74.6)	76 (85.4)	0.095
Smoking: n (%)	12 (19.0)	14 (15.7)	0.593
Allergies: n (%)	43 (68.3)	60 (67.4)	0.913
Diabetes Type 2: n (%)	7 (11.1)	9 (10.1)	0.843
CAD: n (%)	5 (7.9)	11 (12.4)	0.381
Hypertension: n (%)	24 (38.1)	25 (28.1)	0.194
High Cholesterol: n (%)	14 (22.2)	25 (28.1)	0.415
Prior Heart Failure: n (%)	1 (1.6)	1 (1.1)	0.805
Current Depression: n (%)	16 (25.4)	28 (31.5)	0.417
MRC Dyspnea Scale: Mean (SD)	2.2 (1.12)	1.9 (0.82)	0.082
Prior PFT: n (%)	31 (49.2)	47 (52.8)	0.662
Prior Chest x-ray: n (%)	30 (47.6)	42 (47.2)	0.598
Prior Echo: n (%)	8 (12.7)	14 (15.7)	0.601
Prior ECG: n (%)	27 (42.9)	34 (38.2)	0.564
Prior Methacholine: n (%)	0 (0)	2 (2.2)	0.231
Previously given a diagnosis for SOB symptoms: n (%)	34 (54.0)	46 (51.7)	0.781
Systolic (mean)	125.92	123.34	0.522
Diastolic(mean)	76.79	76.43	0.884

*Significant Level $P < 0.05$.

SD: Standard Deviation, Yrs: years; COPD: Chronic Obstructive Pulmonary Disease; CAD: Coronary Artery Disease; MRC: Medical Research Council; PFT: Pulmonary Function Test; Echo: Electrocardiogram; ECG: Echocardiography.

[§]Subjects attending community pharmacies who declined to perform PiKo-6 but agreed to participate in the study and performed a laboratory pulmonary function test.

As noted from Table 4.1, there was no major statistically significant difference between patients who volunteered or declined to perform the PiKo-6 spirometry in pharmacy settings. Also, there was no statistically significant difference observed when patients who were recruited from the pharmacy setting (n=234) were compared to patients who were identified in the community setting through the use of the pharmacy databases (n=241). The sample characteristics of the patients who attended the community pharmacies and patients in the community (recruited via the pharmacy records) are summarized in Appendix 3.

The demographics of the patients who volunteered to perform the PiKo-6 were the following: 52.4 % were men, and the median age was 50.2 years. The mean \pm Standard Deviation (SD) age of the sample was 53.9 ± 15.3 years, with a mean BMI of 31.9 ± 7.40 kg/m². Participants were primarily Caucasian (74.6%). Most of the patients suffered from allergies (68.3%), but only 19.0% of the patients were current smokers. The majority of the volunteers had a history of Asthma (60.3%), but only 17.5% had a history of COPD.

The most common self-reported comorbidities amongst the population were hypertension (38.1%), depression (25.4%), high cholesterol (22.2%), and Type 2 Diabetes (11.1%); alternatively, coronary artery disease and HF were reported at 7.9% and 1.6%, respectively. About half of the patients (54%) that perform the PiKo-6 in the pharmacy setting stated that they had a previous diagnosis for their SOB symptoms by their family physician. Of the 63 patients that performed the PiKo-6, 42.9% were diagnosed with asthma and 10% were diagnosed with COPD. Furthermore, subjects were asked “Have you ever had any of the following tests for your SOB symptoms?”. The most common reported tests were pulmonary function tests (49.2%), chest x - rays (47.6%), electrocardiograms (42.9%), and echocardiographies (12.7%).

The Medical Research Council (MRC) scale measures disability caused by breathlessness. It consists of five grades: grade 1, “Not troubled by breathlessness except on strenuous exercise”; grade 2, “Short of breath when hurrying or walking up a slight hill”; grade 3, “Walks slower than contemporaries on the level because of breathlessness, or has to stop for breath when walking at own pace”; grade 4, “Stops for breath after about 100 m or after a few minutes on the level”; grade 5, “Too breathless to leave the house, or breathless when dressing or undressing” (Stenton, 2008). The majority of patients (63.5%) reported dyspnea scores of 1 and 2, whereas 36.5 % of the enrolled patients reported dyspnea scores from 3 to 5 that they fulfilled the criteria for referral to a hospital-based rehabilitation program.

4.2 Repeatability of the PiKo-6

The repeatability of PiKo-6, variation in consecutive measurement on the same subject, was explored. Patients performed two tests using the PiKo-6 spirometry, within a five minute interval, to measure the repeatability coefficient. There was a strong correlation between the first and second Piko-6 measurements of pFEV₁ ($r = 0.835$, $P < 0.001$; Figure 4.2) and pFEV₆ ($r = 0.872$, $P < 0.001$). There was a weaker but significant correlation between the first and second Piko-6 measurements of pRatio ($r = 0.664$, $P < 0.001$; Figure 4.3). ICC were: 0.83 ($p < 0.001$) for pFEV₁, 0.87 ($p < 0.001$) for pFEV₆, and 0.61 ($p < 0.001$) for pRatio. These values show a strong correlation between the PiKo-6 consecutive measurements as suggested by the Fleiss, John Wiley & Sons, 1986 threshold values. Mean (\pm SD) of PiKo-6 spirometry (FEV₁, FEV₆, and Ratio) and ICC are presented in Table 4.2.

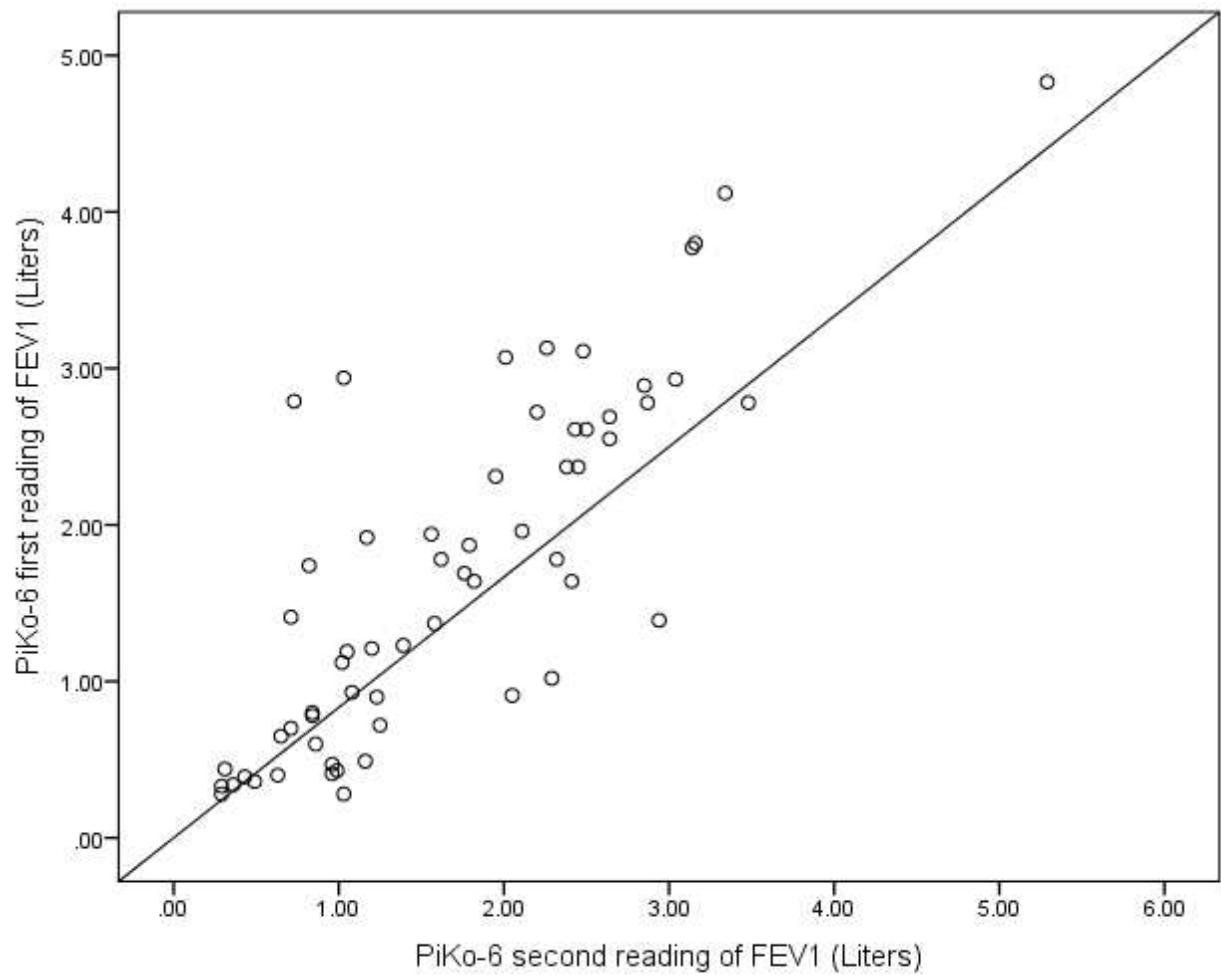


Figure 4.2 The correlation of pFEV₁ spirometry measured with the PiKo-6 in the first reading compared to the second reading.

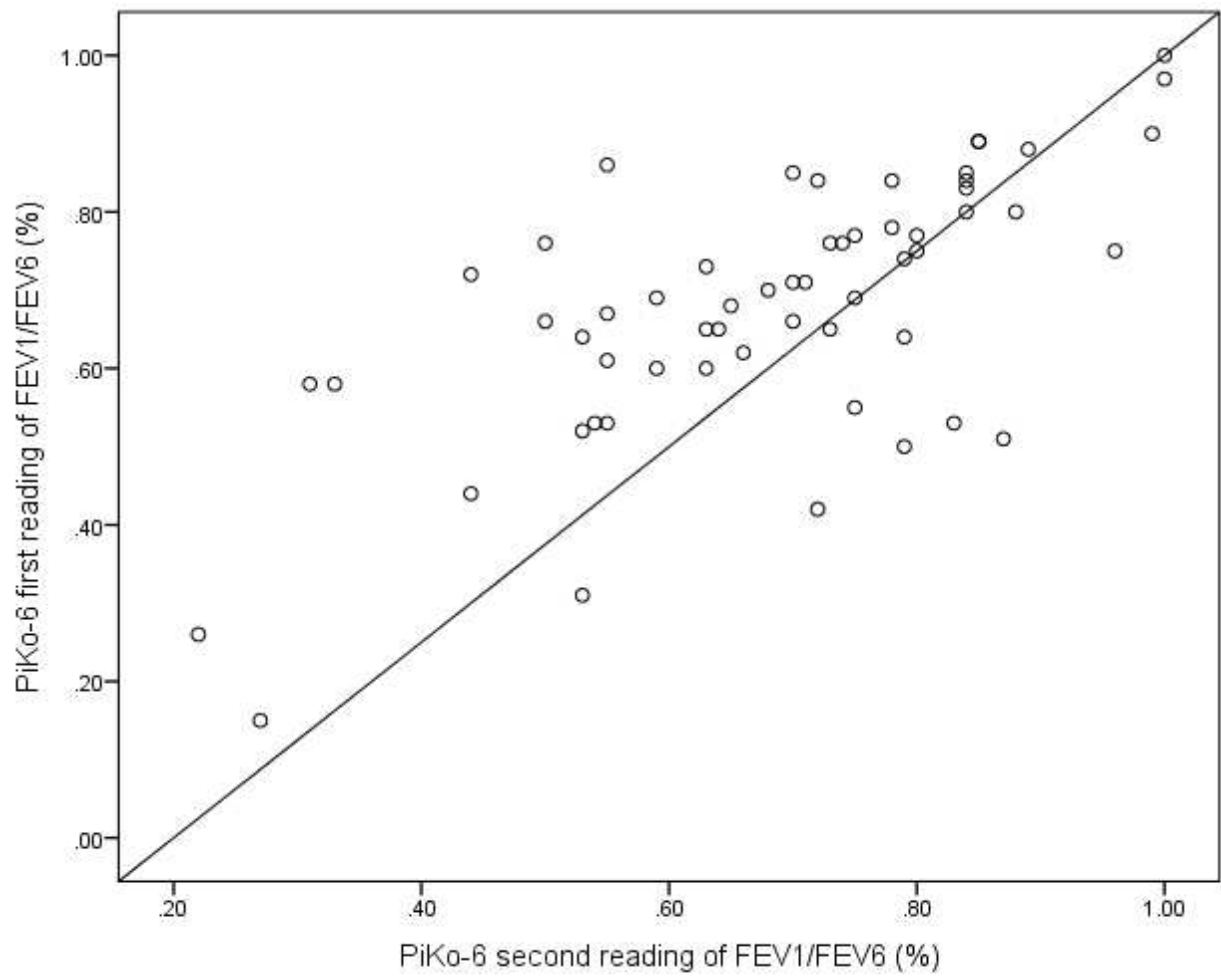


Figure 4.3 The correlation of pRatio measured with the PiKo-6 in the first reading compared to the second reading.

Table 4.2 *Mean (\pm SD) of PiKo-6 spirometry (FEV₁, FEV₆, and Ratio) and Intraclass Correlation coefficient.*

	PiKo-6 Spirometry	Test 1	Test 2	ICC	95% Confidence Interval
All patients	FEV ₁ , Liters	1.69 \pm 1.12	1.69 \pm 1.00	0.83	0.74 – 0.90
(n= 63)	FEV ₆ , Liters	2.47 \pm 1.42	2.57 \pm 1.36	0.87	0.80 – 0.92
	FEV ₁ /FEV ₆	0.68 \pm 0.16	0.68 \pm 0.17	0.61	0.43 – 0.85
<i>Physician-diagnosed outcomes</i>					
Asthma	FEV ₁ , Liters	1.75 \pm 1.23	1.84 \pm 1.00	0.72	0.78 - 0.86
(n=26)	FEV ₆ , Liters	2.71 \pm 1.45	2.93 \pm 1.39	0.76	0.55 – 0.88
	FEV ₁ /FEV ₆	0.65 \pm 0.20	0.66 \pm 0.17	0.94	0.87 – 0.97
COPD	FEV ₁ , Liters	1.31 \pm 0.75	1.24 \pm 0.66	0. 86	0.67 – 0.95
(n=19)	FEV ₆ , Liters	2.00 \pm 1.09	2.01 \pm 0.95	0.90	0.75 – 0.96
	FEV ₁ /FEV ₆	0.65 \pm 0.10	0.61 \pm 0.13	0.70	0.36 – 0.89
Others	FEV ₁ , Liters	1.99 \pm 1.21	1.96 \pm 1.19	0. 96	0.88 – 0.97
(n=18)	FEV ₆ , Liters	2.62 \pm 1.61	2.62 \pm 1.57	0.92	0.71 – 0.97
	FEV ₁ /FEV ₆	0.75 \pm 0.15	0.77 \pm 0.18	0.13	-0.33 – 0.57

FEV₁: Forced Expiratory Volume in one second, FEV₆: Forced Expiratory Volume in six seconds, ICC: Intra Class Correlation.

4.3 Validity of the PiKo-6

All patients who performed the PiKo-6 spirometry were referred to perform a laboratory PFT. In all cases, the standard laboratory PFT was performed. The median of the time difference between PiKo-6 spirometry and standard laboratory spirometry was 35 days (interquartile range: 18 – 77). We compared the results of the pre and post bronchodilator (BD) PFT (spirometry, lung volumes, and diffusion capacity) in relation to differences across physician diagnosis. Mean (\pm SD) of percent (%) predicted pre-BD laboratory PFT results are shown in Table 4.3 and post-BD laboratory PFT results are shown in Table 4.4.

Table 4.3: Mean (\pm SD) of percent (%) predicted pre- bronchodilator laboratory Pulmonary Function Test

Pre-BD	All patients (n=63)	Asthma (n=26)	COPD (n=19)	Others (n=18)	pValue
FVC,	94.38\pm20.29	101.11\pm15.97	81.94\pm15.68	97.77\pm24.73	.004
FEV₁,	80.36\pm22.84	87.46\pm15.57	59.31\pm14.67	92.33\pm24.38	.000
*FEV₁/FVC ratio, %	68.17\pm11.62	70.30\pm08.79	57.05\pm10.49	76.83\pm06.19	.000
PEF	96.33\pm28.10	101.22\pm26.43	74.21\pm22.05	112.55\pm21.80	.000
VC	96.77 \pm 20.13	103.26 \pm 14.57	85.36 \pm 18.19	99.44 \pm 24.44	.008
TLC	103.38 \pm 17.24	105.07 \pm 15.65	107.78 \pm 18.06	96.27 \pm 17.30	.102
RV	100.04 \pm 36.20	91.61 \pm 30.71	129.73 \pm 31.78	80.88 \pm 29.01	.000
RV/TLC	95.04 \pm 28.63	85.23 \pm 22.22	119.84 \pm 22.03	83.05 \pm 27.63	.000
FRC PL	98.42 \pm 23.73	98.46 \pm 21.27	110.89 \pm 25.20	85.22 \pm 18.89	.003
DLCO	93.19 \pm 22.20	97.15 \pm 17.52	79.36 \pm 20.72	102.05 \pm 23.88	.003
VA,	88.88 \pm 15.16	93.92 \pm 12.84	80.68 \pm 14.71	90.27 \pm 15.83	.011
DLCO adjusted for VA	97.84 \pm 21.07	99.53 \pm 15.45	86.31 \pm 21.26	107.55 \pm 23.16	.006

BD: Bronchodilator, FVC: Forced Vital Capacity, FEV₁: Forced Expiratory Volume in one second, PEF: Peak Expiratory Flow, VC: Vital Capacity, TLC: Total Lung Capacity, RV: Residual Volume, FRCPL: Functional Residual Capacity Plain phase, DLCO: Diffusing Capacity, VA: Alveolar Volume

* Values base on Mean (\pm SD) of actual pre-bronchodilator laboratory PFT (spirometry)

-Bolded values were available for post-bronchodilator and used in the diagnosis of asthma and COPD by ATS and ERS guideline, and in aide of physician assessment. The data are presented in Table 4.4

Table 4.4: Mean (\pm SD) of percent (%) predicted post- bronchodilator laboratory Pulmonary Function Test

Post-BD	All patients (n=63)	Asthma (n=26)	COPD (n=19)	Others (n=18)	pValue
FVC	95.12 \pm 95.12	99.23 \pm 26.06	87.15 \pm 16.11	97.61 \pm 23.36	.191
FEV ₁	83.60 \pm 24.70	89.19 \pm 24.60	65.31 \pm 14.28	94.83 \pm 23.74	.000
*FEV ₁ /FVC ratio, %	69.98 \pm 12.71	71.46 \pm 12.74	59.26 \pm 09.57	79.17 \pm 05.69	.000
PEF	99.68 \pm 30.28	102.15 \pm 33.87	81.42 \pm 16.79	115.38 \pm 26.76	.002

FVC: Forced Vital Capacity, FEV₁: Forced Expiratory Volume in one second, FEV₆: Forced Expiratory Volume in six seconds, PEF: Peak Expiratory Flow.

* Values base on Mean (\pm SD) of actual post-bronchodilator laboratory PFT (spirometry)

To assess the validity of the PiKo-6 spirometer, we compared pFEV₁, pFEV₆, and pRatio with pre-BD FEV₁, FVC, and FEV₁/FVC, respectively. Because the PiKo-6 tests were conducted in community pharmacy settings, the pharmacists did not use bronchodilators when obtaining PiKo-6 measurements. A two-sided, paired t-test was used to assess the differences between the PiKo-6 and laboratory spirometers. Differences were considered statistically significant at $P < 0.05$. There was a statistically significant, moderately positive correlation between measurements of pFEV₁ by PiKo-6 and FEV₁ by laboratory spirometry ($r = 0.63$, $P < 0.001$; Figure 4.4); and pFEV₆ and FVC ($r = 0.66$, $P < 0.001$); and between measurements of pRatio and FEV₁/FVC ($r = 0.58$, $P < 0.001$; Figure 4.5).

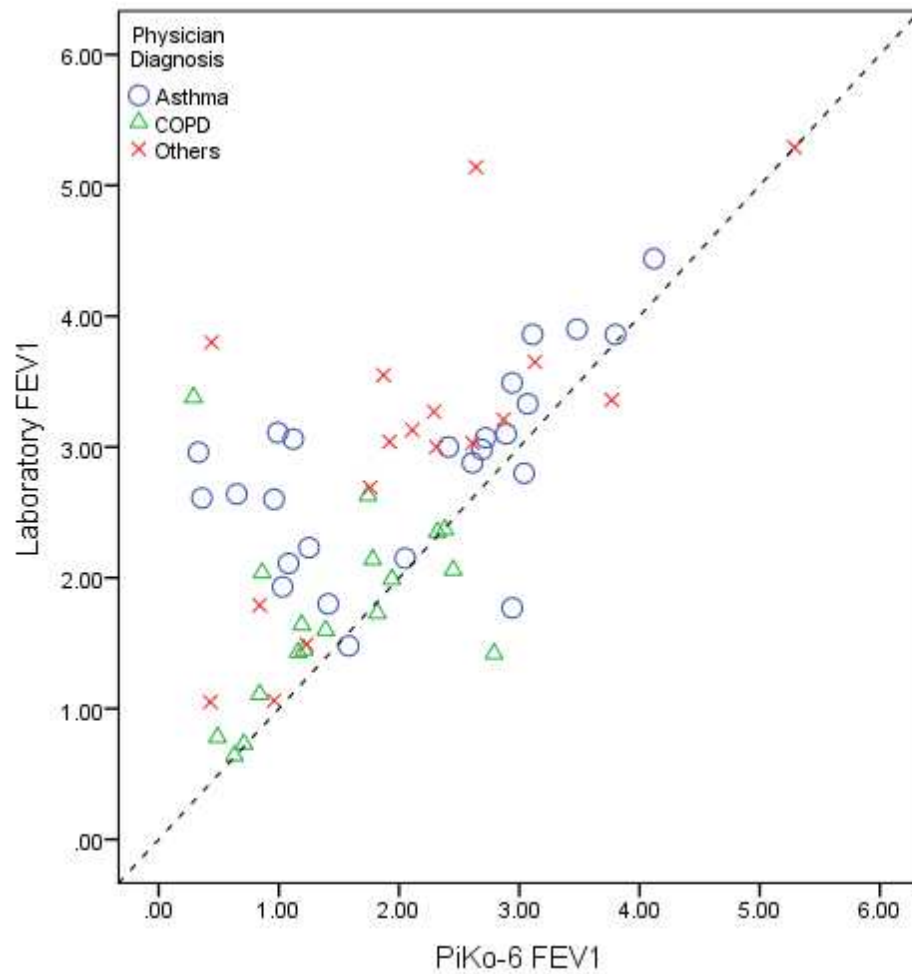


Figure 4.4 The correlation of pFEV₁ (Litres) measured with the PiKo-6 compared to the FEV₁ (Litres) measured with the Laboratory Spirometry (pre-bronchodilator).

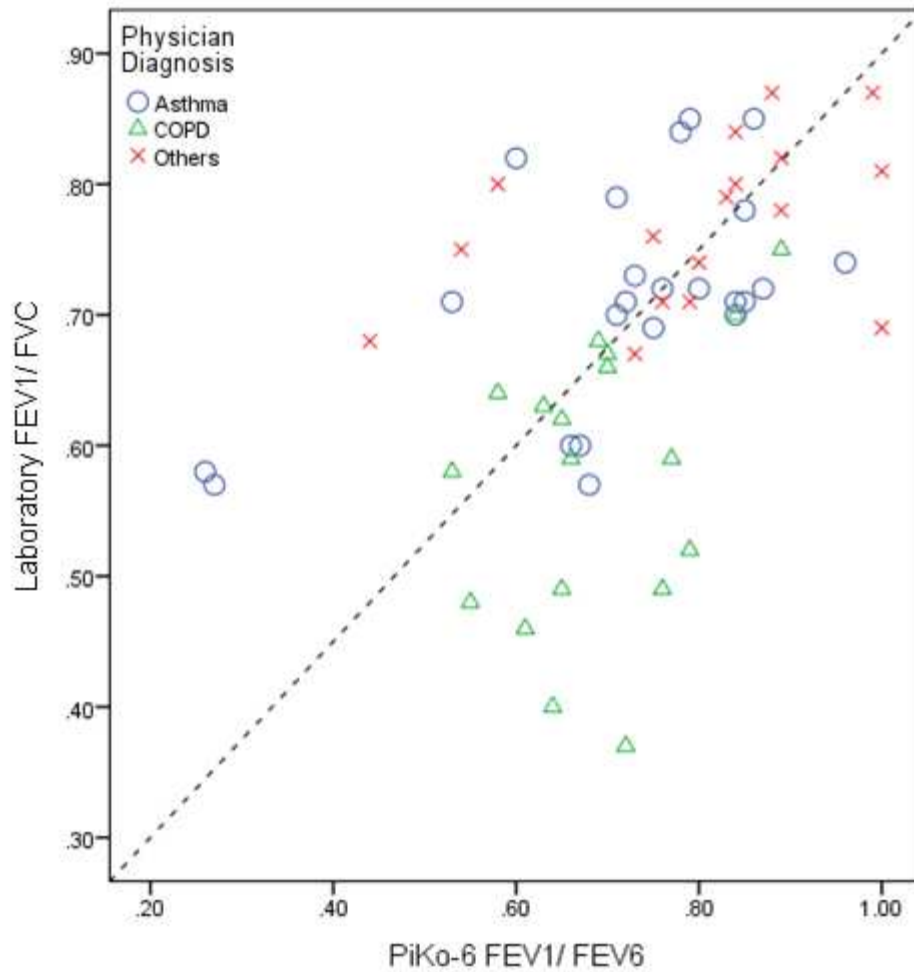


Figure 4.5 The correlation of $\text{pFEV}_1/\text{pFEV}_6$ measured with the PiKo-6 compared to the FEV_1/FVC measured with the Laboratory Spirometry (pre-bronchodilator).

Bland-Altman plots were used to compute the agreement between the Piko-6 and standard lab spirometry. The difference against the mean for the pFEV₁ (Figure 4. 6) and the pRatio (Figure 4.7) indicate that the difference between the PiKo-6 spirometry and the laboratory spirometry is not significant enough to cause problems in clinical interpretation. PiKo-6 bias (95% CI) was assessed against laboratory spirometry for pFEV₁ -0.65 (-0.79; 0.01; *p*Value <0.001) and pRatio -0.04 (-0.08; 0.01, *p*Value=0.02). The clinical limits of agreement as measured by the average residual difference from the laboratory PFT spirometry were: pFEV₁ (-1.17 to 2.47 litres), pFEV₆ (-1.26 to 3.14 litres), and pRatio (-0.33 to 0.24). PiKo-6 bias (95% CI) and limits of agreement with standard laboratory spirometry values are illustrated in Table 4.5.

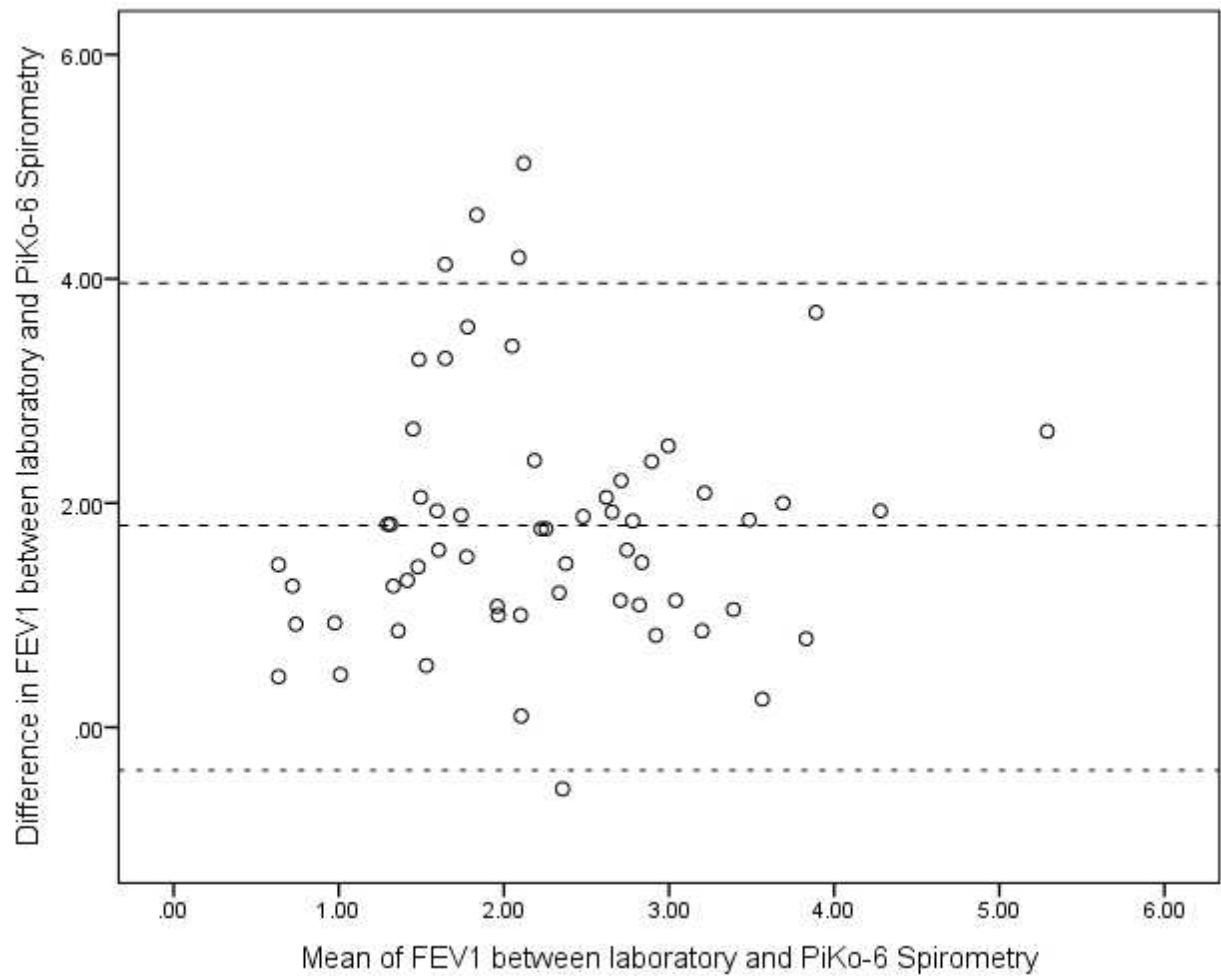


Figure 4.6 **Bland and Altman Plot showing the difference against mean for the pFEV₁ (Litres) measured by the PiKo-6 spirometer compared to the FEV₁ (Litres) measured by the laboratory spirometer (pre-bronchodilator).**

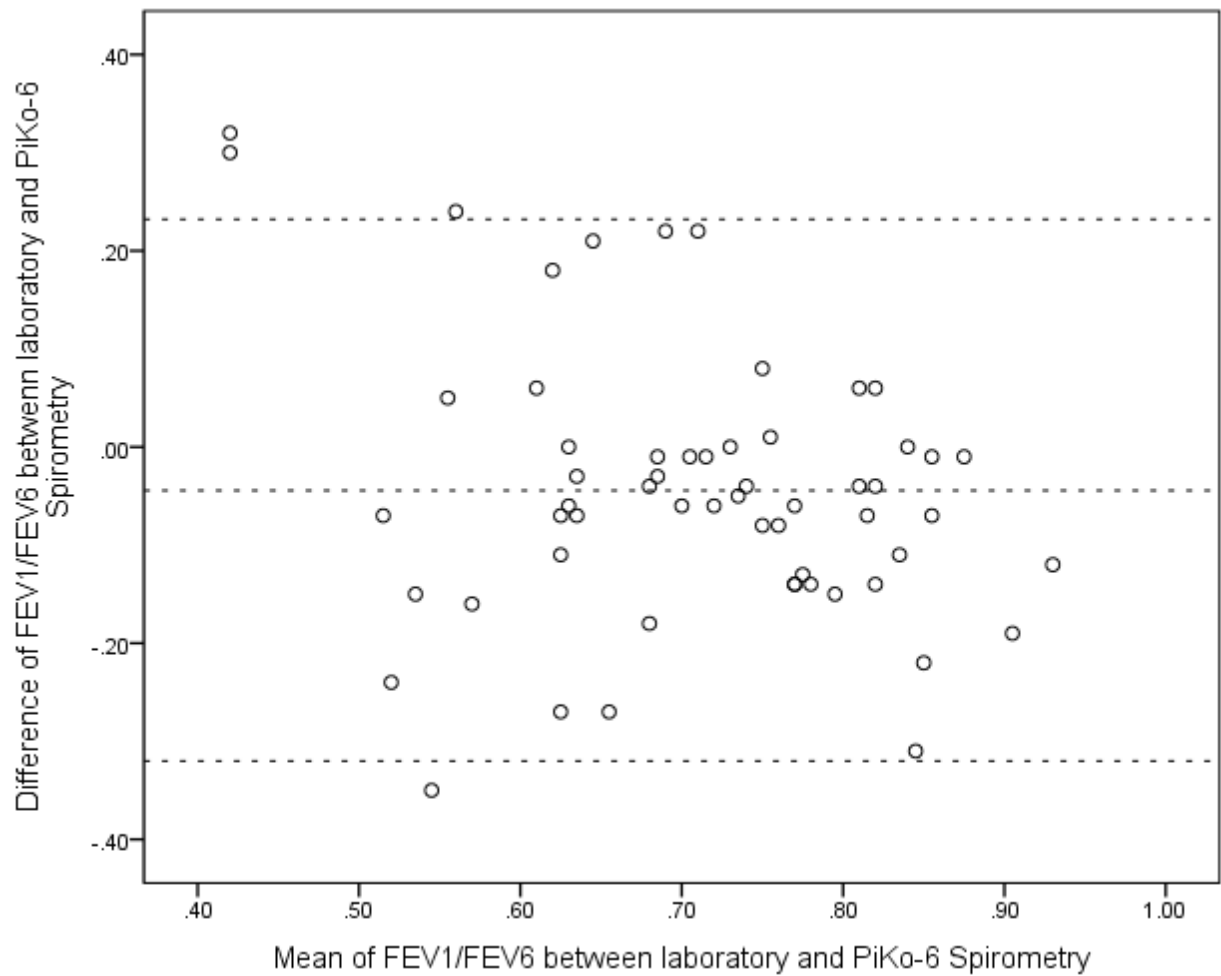


Figure 4.7 **Bland and Altman Plot showing the difference against mean for the $pFEV_1/pFEV_6$ measured by the PiKo-6 spirometer compared to the FEV_1/FVC measured by the laboratory spirometer (pre-bronchodilator).**

Table 4.5 *PiKo-6 bias (95% CI) and limits of agreement with standard laboratory spirometry.*

		Standard PFT Lab Spirometry (FEV ₁ , FVC, FEV ₁ /FVC)		*Limits of Agreement
		Correlation	[‡] Bias (95%CI)	
[§] Maximum effort (from PiKo-6 Test 1 and 2)				
All patients	pFEV ₁	0.629	-0.65(-0.79; 0.01)	-1.17 to 2.47 (L)
(n=63)	pFEV ₆	0.658	-0.94(-1.22;-0.18)	-1.26 to 3.14 (L)
	pRatio	0.478	-0.04(-0.08; 0.01)	-0.33 to 0.24
<i>Physician-diagnosed outcomes</i>				
Asthma	pFEV ₁	0.600	0.74(0.37; 1.11)	-1.06 to 2.54 (L)
(n=26)	pFEV ₆	0.677	0.89(0.48; 1.30)	-1.11 to 2.89 (L)
	pRatio	0.559	0.00(-0.06; 0.06)	-0.15 to 0.28
COPD	pFEV ₁	0.289	0.31(-0.12; 0.73)	-1.43 to 2.04 (L)
(n=19)	pFEV ₆	0.426	0.81(0.28; 1.34)	-1.63 to 2.94 (L)
	pRatio	0.342	-0.11(-0.17;-0.06)	-0.35 to 0.12
Others	pFEV ₁	0.712	0.89(0.42; 1.36)	-0.96 to 2.74 (L)
(n=18)	pFEV ₆	0.668	1.16(0.48; 1.83)	-1.48 to 3.80 (L)
	pRatio	0.441	-0.03(-0.34;-0.20)	-0.31 to 0.26

FEV₁: Forced Expiratory Volume in one second, FEV₆: Forced Expiratory Volume in six seconds.

[‡] For interpretation, refer to ‘Statistical methods for assessing agreement between two methods of clinical measurement’ (Bland & Altman, 1986).

*Small limit of agreement (within $\pm 2SD$) indicate a high agreement of PiKo-6 with standard laboratory spirometry values. The difference within these limits of agreement would not be clinically important.

[§]Patient’s maximum effort performed from PiKo-6 Test 1 & 2 was used for the assessment of agreement with the standard laboratory spirometry.

4.3.1 Sensitivity and specificity analysis in patients with COPD

It is easier to screen for COPD than asthma or other chronic lung diseases, because COPD diagnosis does not require reversibility testing which can only be assessed with post-bronchodilator administration. This is usually not available in community settings. The GOLD guidelines recommend post BD of $FEV_1/FVC < 0.70$ as the cut-off value required to diagnose COPD (GOLD, 2014). Diagnostic accuracies of the standard laboratory FEV_1/FVC and the PiKo-6 pRatio were summarized by calculating sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and the area under the ROC curve (ROC-AUC).

The sensitivity and specificity of the laboratory spirometer pre BD $FEV_1/FVC < 0.70$ offered optimal sensitivity (89%) and specificity (72%). On the other hand, the sensitivity and specificity of the laboratory spirometer post BD $FEV_1/FVC \leq 0.70$, which is the recommended cut off value by ATS/ERS guidelines, offered sensitivity (92%) and specificity (73%) when compared with physician diagnosed COPD. The use of bronchodilator slightly improved the sensitivity and specificity values.

The predictive power of the PiKo-6 pRatio score was calculated using different cut-off values. As mentioned earlier, the pharmacists did not use bronchodilators when obtaining PiKo-6 measurements because the PiKo-6 tests were conducted in community pharmacy settings. The sensitivity and specificity of the PiKo-6 spirometer $pRatio \leq 0.70$ offered sensitivity (52%) and specificity (77%). Alternatively, when raising the cut-off value of the PiKo-6 pRatio to ≤ 0.80 , the sensitivity was 84% and the specificity was 50%. Raising the cut-off value of the PiKo-6 pRatio to ≤ 0.80 improved the sensitivity of the PiKo-6 spirometer. The sensitivity, specificity,

PPV, and NPV are presented for the pRatio and both pre and post FEV₁/FVC at different cut-off values in Table 4.6.

In Figure 4.8, the diagnostic accuracy of the PiKo-6 FEV₁/FEV₆ (pRatio) in discriminating between subjects with or without COPD, as summarised by the ROC-AUC value, was 0.70 (95% CI= 0.56, 0.84). On the other hand, the diagnostic accuracy of the standard spirometer pre BD FEV₁/FVC, as summarised by the ROC-AUC value, was 0.90 (95% CI= 0.81, 0.98).

The GOLD guidelines recommend spirometry value of FEV₁/FVC \leq 0.70 to diagnose COPD (GOLD, 2014). To use the PiKo-6 for screening purposes in community settings, we recommend raising the cut-off value of the PiKo-6 ratio to \leq 0.80. According to the ROC curve (Figure 4.8) and the scatter plot (Figure 4.9), the best combination of specificity and sensitivity corresponded to a PiKo-6 pRatio score of 0.80. Only patients with a pRatio \leq 0.80 could be referred to perform standard laboratory spirometry to confirm airflow obstruction. Although raising the cut-off value of the pRatio to \leq 0.80 would increase the false positive rates (from 23% to 50%), the selected patients could have other OADs that require a standard laboratory PFT to confirm their diagnosis. Figure 4.9 show the cut-off values for the pRatio and pre-BD FEV₁/FVC at \leq 0.70 and \leq 0.80 assessed against physician diagnosis of COPD.

Table 4.6 *Diagnostic accuracy of the PiKo-6 (pRatio) and Laboratory spirometry (FEV₁/FVC) when changing cut-off values and bronchodilator usage (assessed against physician diagnosed COPD).*

	The cut-off value ≤ 0.70			The cut-off value ≤ 0.80		
	PiKo-6 Spirometry	Pre-BD Laboratory Spirometry	Post-BD Laboratory Spirometry ^a	PiKo-6 Spirometry ^b	Pre-BD Laboratory Spirometry	Post-BD Laboratory Spirometry
Sensitivity	0.52	0.89	0.92	0.84	1	1
Specificity	0.77	0.72	0.73	0.50	0.25	0.25
PPV	0.50	0.58	0.50	0.42	0.36	0.36
NPV	0.79	0.94	0.97	0.88	1	1

BD: bronchodilator, FEV₁: Forced Expiratory Volume in one second, FVC: Forced Vital Capacity, pFEV₁: PiKo Forced Expiratory Volume in one second, pFEV₆: PiKo Forced Expiratory Volume in six seconds, PPV: Positive Predictive Value, NPV: Negative Predictive Value

a: The measure used to diagnose COPD according to the GOLD guidelines (GOLD,2014)

b: The PiKo-6 measure proposed to screen for COPD at community pharmacies in the current study

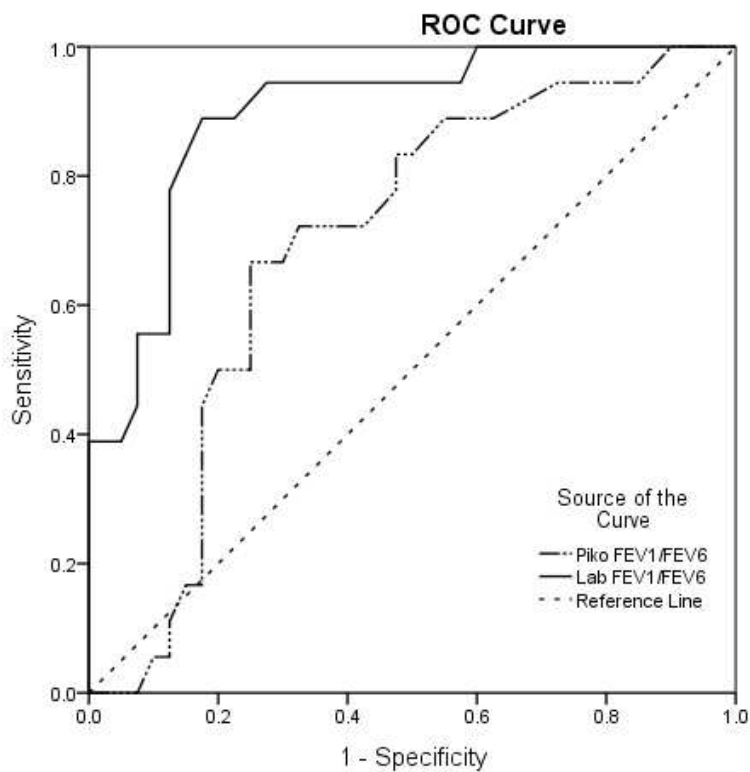


Figure 4.8 The receiver operating characteristic (ROC) curve for the Piko-6 pRatio versus the standard Laboratory pre BD FEV₁/ FVC (Assessed against Physician-diagnosed COPD).

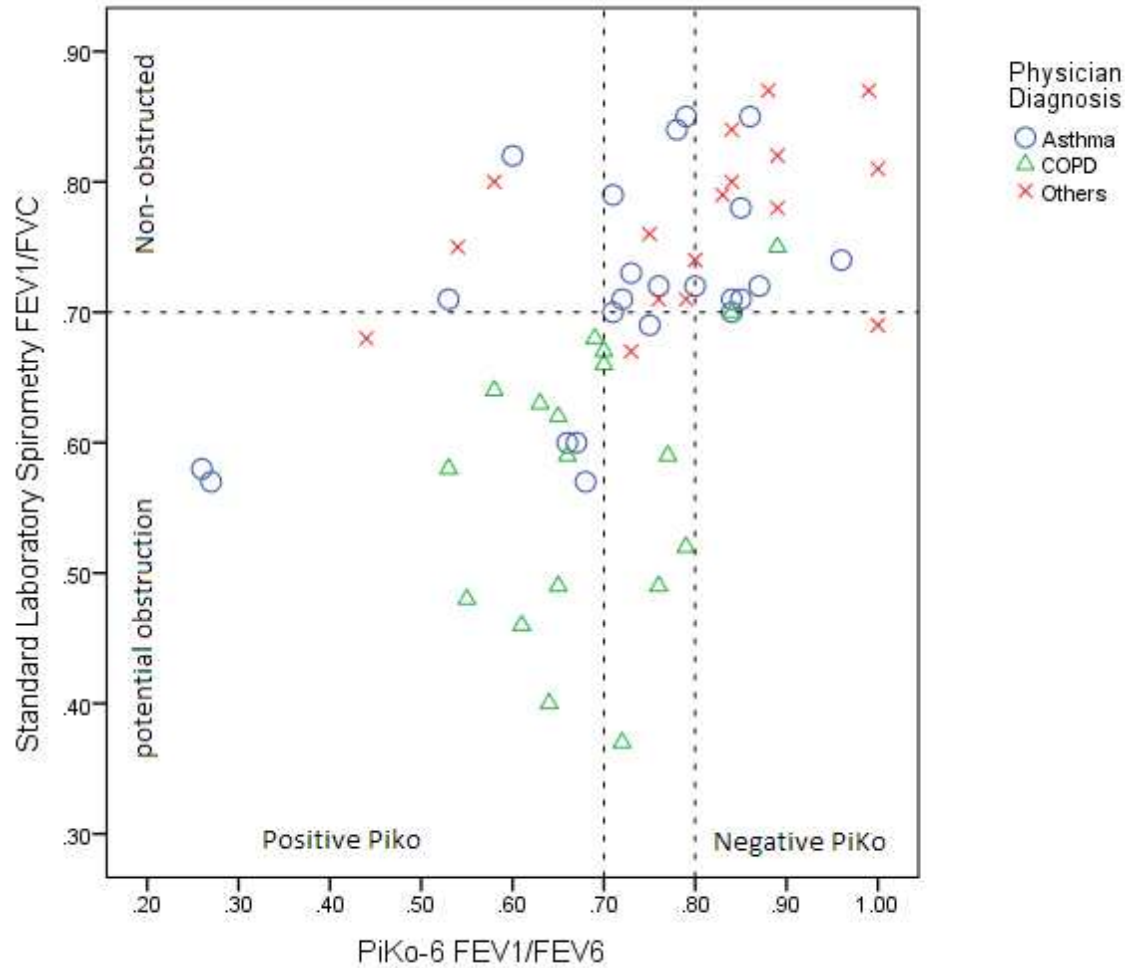


Figure 4.9 **Different cut off values for the pRatio (pFEV₁/pFEV₆) measured with the PiKo-6 compared to the FEV₁/FVC Laboratory Spirometry (pre-bronchodilator).**

The PiKo-6 cut-off values of the pRatio (x-axis) and Laboratory spirometry cut-off values of FEV₁/FVC (y-axis) are outlined. By raising the cut-off value of the PiKo-6 from 0.70 to 0.80, we include more patients who are suspected of having obstructive airway diseases. After performing laboratory spirometry, physicians concluded that most of these patients are diagnosed with COPD and asthma.

Chapter 5: Discussion and Conclusion

5.1 Main findings

In this thesis, the results of the PiKo-6 spirometer were compared with standard pulmonary function tests. In addition, the PiKo-6 was assessed against physician diagnosed COPD to calculate sensitivity, specificity, PPV, and NPV. The comparison shows that the use of the PiKo-6 spirometry could be a method for preselecting subjects for further diagnostic work up of patients who, according to their pharmacist, may have chronic airflow obstruction. The results suggest that the PiKo-6 correlates well with standard laboratory spirometry; thus it could be used to screen for OADs at community pharmacies. We used a screening approach that consisted of a screening questionnaire, followed by a pocket spirometry assessment, then a standard laboratory spirometry. This pharmacy screening approach may improve efficiency of early detection and management of OADs. Nevertheless, the final diagnosis of the OAD will be completed by the family physician.

Taking into account that the NPV of the PiKo-6 spirometry was 88%, a subject with a negative PiKo-6 spirometry test (pre-BD $pRatio \geq 0.80$) is unlikely to show airflow obstruction in subsequent diagnostic spirometry testing. However, the PiKo-6 spirometry should not be used to diagnose COPD. In our study, we suggest choosing a high cut-off value of 80% for the pRatio in patients with SOB symptoms to avoid missing airflow limitation, thus accepting a high rate of false positive results. We suspect that most of the patients, who showed airflow limitation when tested with the PiKo-6 spirometry, are at a high risk of OADs. Our results recommend patients with a PiKo-6 FEV_1/FEV_6 (pRatio) lower than 0.80 to be referred to their family physician for further diagnostic work up, if it was lacking.

5.2 Previously published studies that compared the PiKo-6 spirometry with the standard laboratory spirometry

Solidoro et al., used the PiKo-6 spirometry in a community pharmacy setting; however, they did not compare the results of the PiKo-6 with the standard spirometry which limits the comparability of their results with our study (Solidoro et al., 2013). The study by Solidoro et al. is summarised in section 5.4 below.

Due to the lack of studies that validate the use of the PiKo-6 spirometer in community pharmacy settings, we investigated studies that validated the use of the PiKo-6 in primary care settings. We summarized four cross sectional studies that validated the use of the PiKo-6 in primary care settings. Studies were conducted in Asia (Wada et al., 2010), Europe (Bemt et al., 2014; Kaufmann et al., 2009), and Australia (Frith et al., 2011). All four studies examined the diagnostic accuracy of the PiKo-6 spirometer compared to laboratory spirometry. In addition, investigators using the PiKo-6 were given a uniform and brief training on how to use the PiKo-6 device according to the manufacturer's instructions.

First, our finding that the PiKo-6 spirometer allows simple screening for OADs replicates the findings of a randomized cross sectional study conducted by (Frith et al., 2011). The study was implemented in a primary care setting to determine the accuracy of FEV₁/FEV₆ using the portable PiKo-6 spirometer to screen for COPD. Current and former smokers (> 50 years old) with no previous respiratory diagnosis (case finding [CF]) or with an asthma diagnosis or treatment (differential diagnosis [DD]) were evaluated using validated questionnaires, pre-bronchodilator (BD) FEV₁/FEV₆ and pre and post-BD FEV₁/FVC spirometry. The investigators used a study diagnosis of COPD based on GOLD spirometry criteria, post-BD FEV₁/FVC of < 0.70; In addition, they used a study diagnosis of asthma based on spirometry testing with

bronchodilator reversibility according to ATS/ERS guidelines. The researchers concluded that the PiKo-6 could optimise early referral for spirometry and improve provision of early, targeted interventions aimed at reducing the burden of COPD (Frith et al., 2011). The results of Frith et al. will be compared with the results of our study in in section 5.3.

A second article by Wada et al. designed a cross-sectional study to investigate the usefulness of a combination of the portable PiKo-6 spirometer with a COPD questionnaire to screen patients in a primary care setting (Wada et al., 2010). The researchers included clinically stable outpatients attending a cardiovascular clinic and excluded patients who were <40 years old, those who had already been diagnosed as having COPD, and those receiving treatment for COPD. Patients with both a $pFEV_1/pFEV_6 < 70\%$, as measured on the PiKo-6, and a score of 17 points on the International Primary Care Airways Group (IPAG) COPD questionnaire were assigned to the COPD group, and all other patients were assigned to the non-COPD group. Patients in the COPD group underwent spirometry to confirm their diagnosis. The relationships between $pFEV_1$, $pFEV_6$ and $pFEV_1/pFEV_6$, as measured by the PiKo-6, and FEV_1 , FVC and FEV_1/FVC , respectively, as measured by spirometry, were assessed. Wada et al., concluded that combining both the PiKo-6 portable spirometer with the IPAG COPD questionnaire may be a useful and feasible method for identifying undiagnosed COPD patients attending a cardiovascular outpatient clinic. The results of Wada et al. will be compared with the results of our study in in section 5.3.

The third article by Kaufmann et al., used a cross sectional study to investigate if the PiKo-6 could simplify and improve the diagnosis of so far undiagnosed asthma or COPD in the primary care setting (Kaufmann et al., 2009). The researchers included patients attending primary care practices and excluded patients with any known pulmonary disease. All patients whose

pFEV₁ /pFEV₆ was < 80% were told to be at risk for pulmonary obstruction and were invited to a standardized laboratory PFT. If the standardized PFT was 'normal', patients underwent a standardized bronchial challenge testing using methacholine to identify patients with asthma. Asthma was defined as follows: respiratory symptoms (e.g. cough, dyspnea or phlegm) and \geq 20% decline in FEV₁ following methacholine provocation or an acute reversibility of > 200 ml FEV₁ or > 15% after bronchodilation. COPD was defined as follows: reversibility of FEV₁ \leq 200 ml or < 15% after bronchodilation. Kaufmann et al. concluded that the PiKo-6 may improve the detection rate of undiagnosed airflow limitation in the primary care setting (Kaufmann et al., 2009). The results of Kaufmann et al. will be compared with the results of our study in in section 5.3.

Lastly, a recent cross-sectional study by Bemt et al. has presented data to assess the diagnostic utility of the PiKo-6 relative to a standard laboratory spirometry (Bemt et al., 2014). Participants were recruited as they visit a diagnostic centre for a spirometry test based on a referral by their GP for respiratory symptoms that may suggest underlying COPD. Bemt et al., included subjects who were 50 years or older and were current or former smokers. The investigators excluded subjects who performed a spirometry test in the previous 5 years or subjects who have already been diagnosed with COPD. All participants filled out a questionnaire about possible previous diagnoses of chronic respiratory conditions, cigarette smoking, respiratory medication use, previous spirometry tests, and reasons for referral by their GP. In addition, subjects performed standard laboratory spirometry and PiKo-6 spirometry (before and after administration of bronchodilator) during the same visit to the diagnostic centre. The investigators used a post-BD FEV₁/FVC value of 0.70 from a standard laboratory spirometry as the gold standard to diagnose COPD. The researchers compared pre-BD pFEV₁ /pFEV₆, as

measured with the PiKo-6 spirometer, with a post-BD FEV₁ /FVC from diagnostic spirometry. Bemt et al., concluded that the pre-BD Piko-6 spirometry seems to be able to reliably preselect patients for further assessment of airflow obstruction by means of laboratory spirometry (Bemt et al., 2014). Furthermore, they stated that the use of the PiKo-6 spirometry alone would result in overestimation of airflow obstruction and should not replace regular spirometry when diagnosing COPD in primary care settings (Bemt et al., 2014). The results of Bemt et al. will be compared with the results of our study in section 5.3.

5.3 Interpretation of findings in relation to previously published work

In summary, the previously mentioned studies indicated that the PiKo-6 may provide health care workers with a simple, reliable, and practical method for screening patients who might be at risk of OADs. In addition, the PiKo-6 could be used jointly with validated questionnaires as simple screening tools to increase the possibility of early and accurate detection of OADs. Although these studies provide us with some valuable insights, more studies in community pharmacies would be required to confirm the findings and elaborate on suitable cut-off points for the pRatio.

5.3.1 Baseline Characteristics compared to previously published work

Overall, the current literature appears to indicate that the PiKo-6 may be useful in screening patients with OADs. At the time, there was paucity of studies assessing the reliability of the PiKo-6 in North America. To our knowledge, this is the first study that assessed the validity of the PiKo-6 as a screening device in community pharmacy settings by comparing it with standard laboratory spirometry. In this study, we assessed airflow limitation in adults attending community pharmacies with SOB as an important symptom for predicting the onset of

OADs. Sansores et al. stated that there is a high frequency of SOB among patients with airflow limitation (Sansores et al., 2013). In addition, SOB has showed a statistically significant increase in patients with airflow limitation (Kaufmann et al., 2009).

In the previous studies discussed in section 5.2, some studies excluded patients with respiratory diseases (Wada et al., 2010; Kaufmann et al. 2009); alternatively, other researchers included patients with respiratory diseases (Frith et al., 2011; Bemt et al., 2011). The main objective of our study is to assess the validity of the PiKo-6 in patients with suspected OADs. As a result, we included subjects who were prescribed inhalers for their SOB symptoms by their GP to increase the prevalence of respiratory diseases in our study. Similar to the current study, two studies performed both laboratory and PiKo-6 spirometry on all the subjects (Frith et al., 2011; Bemt et al., 2011). Wada et al. and Kaufmann et al. investigated the feasibility of using both COPD diagnostic questionnaires and PiKo-6 measurements to screen patients for COPD (Wada et al., 2010; Kaufmann et al. 2009). However, only patients at risk of pulmonary obstruction were invited to perform a standard PFT (Wada et al., 2010; Kaufmann et al. 2009).

The use of questionnaires has been suggested as the simplest screening method for increasing early COPD detection (Sichletidis et al., 2011). Nevertheless, current COPD screening questionnaires may exclude patients with early stages of COPD because they require symptoms to be present to indicate risk. Fueller et al. found that the ‘COPD Population Screener Questionnaire’ excluded 75% of patients with airflow limitation. This would prevent them from going further to testing with spirometry (Fuller et al., 2012). Studies suggested that the absence of symptoms may mask a diagnosis of obstructive pulmonary diseases. Moreira stated that the odds of under diagnosis were significantly higher among individuals with fewer respiratory symptoms, suggesting that many asymptomatic patients had COPD (Moreira et al., 2014). Early

diagnosis for the underlying disease is poor due to patients having to perform a PFT. Spirometry is required to diagnose the two main diseases, asthma and COPD, underlying the symptoms of SOB.

5.3.2 Repeatability of the PiKo-6 compared to previously published work

The previous studies did not assess the repeatability of the Piko-6 spirometer. In the current study, patients performed two tests using the PiKo-6 spirometry to measure the repeatability coefficient. There was a strong correlation between the first and second Piko-6 measurements of pFEV₁ and pFEV₆; however, there was a weaker but significant correlation between measurements of pRatio. In the current study, pharmacists were trained by pulmonary specialist to perform the PiKo-6 spirometer. The repeatability of the PiKo-6 showed a strong correlation in repeated measurements.

5.3.3 Validity of the PiKo-6 compared to previously published work

The validity of the Piko-6 was assessed by comparing the statistical differences in the results between the PiKo-6 spirometry and the standard laboratory spirometry measurements, for the same subjects. Frith et al., indicated that there were no statistically significant differences between the PiKo-6 mean pre-BD pRatio (pRatio= 0.717) or the standard laboratory spirometry mean ratio (FEV₁/FVC= 0.721), P-value = 0.64 (Frith et al., 2011). Furthermore, Wada et al. (2010) stated that there was a strong correlation between measurements of pre-BD pFEV₁ and pre-BD FEV₁ (r = 0.865, P < 0.001) and between measurements of pre-BD pFEV₆ and pre-BD FVC (r = 0.751, P < 0.001). There was a weaker but significant correlation between pre-BD pRatio and pre-BD FEV₁/FVC, as assessed by spirometry (r = 0.57, P < 0.001) (Wada et al., 2010).

Data from the Frith et al. and Wada et al. studies suggested a good correlation when compared the PiKo-6 with the standard spirometer (Frith et al., 2011; Wada et al., 2010). In the current study, there was a statistically significant, moderately positive correlation between measurements of pre-BD pFEV₁ and pre-BD pFEV₁ ($r = 0.63$, $P < 0.001$); pre-BD pFEV₆ and pre-BD FVC ($r = 0.66$, $P < 0.001$); and between measurements of pre-BD pRatio and pre-BD FEV₁/FVC ($r = 0.58$, $P < 0.001$). This may suggest that, trained pharmacists succeeded in performing the PiKo-6 spirometry in community patients with SOB symptoms. To improve the correlation between Piko-6 and laboratory spirometers, we suggest that future studies should concentrate on training pharmacists on performing portable spirometry.

5.3.4 The PiKo-6 FEV₁/FEV₆ Cut-off values compared to previously published work

Previous studies have suggested different cut-off values for the pRatio. The researchers chose the following values to detect airflow obstruction in primary care settings: <0.73 (Bemt et al., 2014), <0.70 (Wada et al., 2010) and <0.75 (Frith et al., 2011). In our study, we suggest the use of pre-BD pRatio <0.80 as the cut-off value to indicate airway diseases. This value has been recommended as the preferred alternative for post-BD FEV₁/FVC <0.70 as suggested by the guideline diagnosis (Kaufmann et al., 2009).

Studies suggest further investigation of the cut-off values of the pRatio (Sichletidis et al., 2011; & Wada et al., 2010). As a screening tool, we have chosen the high cut-off value of 80% for the pRatio for three reasons. The first is to ensure that we have included a maximal amount of patients with airflow limitation. As a result, we accept the possibility of a high rate of false-positive results because it is more important to include patients with obstructive diseases than to exclude patients that do not have obstructive diseases. Although raising the cut-off value of the

pRatio to ≤ 0.80 would increase the false positive rates (from 23% to 50%), the selected patients could have other OADs that require a standard laboratory PFT to confirm their diagnosis. The second reason is that using FEV₆ instead of FVC may underestimate the airflow limitation because some patients may need longer than six seconds to achieve FVC (Kaufmann et al., 2009). The third reason is that we did not use bronchodilators before testing the patients with spirometry. The current guidelines for Asthma and COPD recommend the use of bronchodilators when performing spirometry (GINA, 2014 & GOLD, 2014). The use of bronchodilators decreases the FEV₁/FVC ratio, especially in patients with asthma. In the current study, we did not use bronchodilators because the aim of our study is to screen the patients and not diagnose them. Adding the use of bronchodilators to the screening process could affect the feasibility and convenience of our screening method. Further research is necessary to elaborate on the factors that affect cut-off values.

The NPV best reflects the purpose that the PiKo-6 spirometry can have in community pharmacy settings: to preselect candidates for full diagnostic spirometry in order to avoid unnecessary testing. In our study, the NPV of the pre-BD pRatio (88%) was slightly different from the NPVs reported by Bemt et al. and Frith et al. who reported NPV values of 94.4% and 91%, respectively. Frith et al. (2011) chose a cut-off point corresponding to pre BD pRatio < 0.75 that offered sensitivity (81%) and specificity (71%). Kaufmann et al. (2009) stated that the present analysis of the distribution of pFEV₆ and pRatio revealed a sensitivity (40.35%) and specificity (100%). Dissimilarities with the previous studies are due to the differences in subject recruitment. In addition, the previous studies compared the results of the PiKo-6 against the standard spirometry to calculate sensitivity, specificity, PPV, and NPV. There are patients who have fixed airway obstruction according the standard spirometry but do not have COPD. Using

only the standard spirometry for diagnosis may label patients as COPD when they are obstructed for other reasons. These reasons may be available in their medical history. As a result, we calculated sensitivity, specificity, PPV, and NPV by comparing the results of the PiKo-6 against physician diagnosed COPD (who used a standard spirometer to confirm the COPD diagnosis).

5.4 The PiKo-6 use in community pharmacy settings

In a recent study by Solidoro et al., customers of 500 pharmacies in Italy were recruited to find probability of obstruction and restriction (Solidoro et al., 2013). Trained pharmacists used the PiKo-6 spirometer, without using a bronchodilator, to test the subjects and collected information about gender, age, height, weight, smoking status, pharmacology. Pharmacists included customers aged between 10-86 years. The aim of the study was to assess the role of pharmacists in screening for obstructive and restrictive lung diseases.

Pharmacists obtained the highest value of three pRatio measures. Customers were considered probably obstructed if the pRatio was $<70\%$ and probably restricted in the $pFEV_6$ was $<75\%$ of the FVC predicted according to the anthropometric data (Solidoro et al., 2013). Solidoro et al., stated that patients suspected of suffering from an obstructive lung disease and show an obstruction when tested by the PiKo-6 spirometer should be referred to a specialist to confirm their diagnosis (Solidoro et al., 2013). The investigators concluded that the PiKo-6 is a valid screening tool for the detection of possible airway obstruction and restriction in a pharmacy setting. Solidoro et al. stated that this approach could reduce the costs on the health care system, enhance prescription appropriateness, and reduce medical visits (Solidoro et al., 2013).

5.5 Strengths and limitations of the current study

The PiKo-6 spirometry and standard laboratory spirometry were completed by different professionals and therefore, the effect of possible learning effect of previous blows was minimised. The median of the time difference between PiKo-6 spirometry and standard laboratory spirometry was 35 days (interquartile range: 18 – 77). Data on these subjects were used for analysis as the effect of this time gap was considered negligible.

Subjects were prescribed medications for their OADs. As shown, there were several differential diagnoses for their medication prescription, of which the largest part (n = 26/63) consisted of ‘Asthma’. ‘COPD’ was another recurring indications for medication prescription (n = 19). For GPs it is difficult to differentiate between COPD and asthma, given the significant overlap in the clinical presentation of these two conditions. The current study may have been biased as the recruited subjects were seeking medications for their breathing problems. The prevalence of disease is likely higher than the general population which will improve the screening utility.

Withholding of medication was not enforced because the study aimed to approximate the ‘real-life’ use of the device for opportunistic-targeted screening. As there was no instruction to withhold bronchodilator medication, there is a possibility that the study included subjects with well-controlled or inactive asthma, subjects with only minor obstructive changes, or subjects with asthma who had taken their bronchodilator before their visit.

There were some statistically significant differences observed in the baseline characteristic between the patients who were recruited from the pharmacy records, community patients, and patients who volunteered to perform the PiKo-6 spirometry in community

pharmacies. These differences could be attributed to the limited sample size. The sample characteristics of the patients who attended the community pharmacies and patients in the community who were recruited via the pharmacy records are summarized in Appendix 3.

In this study we assessed the repeatability of the PiKo-6 device. To our knowledge, there are no published reports about the repeatability of this particular device. However, our results cannot be generalized to other portable spirometers other than the PiKo-6. Another limitation is that we did not have information about the quality and reproducibility of the full laboratory spirometry measurements. The PFT laboratory saved only the best FEV₁ and FVC values in their database, thus we relied on the professional judgement of the lung function staff at the primary care diagnostic centre. Only half of the pharmacists that were invited to participate in the study agreed to participate in the study. This could introduce a limitation of this study as the pharmacy participation rate may not allow for the generalizability of the results.

5.6 Implications for future research and practice

The algorithm used in this study suggested that, if the patient is suspected of having an airway obstruction from the use of the PiKo-6 spirometry in a community pharmacy, the pharmacist will notify the patient's primary care physician for a complete diagnostic workup. Although we recruited patients who are seeking medication for their breathing problems, we recommend that future studies could focus on patients presenting with risk factors for airway diseases and patients who were not tested with spirometry in the past.

To our knowledge, this was the first validation study to determine the validity of the portable PiKo-6 spirometer in a community pharmacy setting. Given the findings from this study, we suggest that, the PiKo-6 spirometry could provide pharmacists with a simple method to

preselect patients for further diagnostic workup by their GPs, if it was lacking. The simplicity of the PiKo-6 spirometry may be able to fit into the tight work schedule of the pharmacists.

The PiKo-6 spirometry may facilitate early, targeted pharmaceutical interventions aimed at reducing the burden of COPD. The effectiveness of such pharmaceutical interventions needs to be evaluated as well, as robust evidence on this issue is currently lacking. Further studies are recommended to assess the role of the pharmacists in screening and management of patients with OADs. In addition, future studies should consider the cost utility analysis and the effects on the patient's quality of life, hospital admissions, and early discharge.

Confirmative diagnostic spirometry remains essential among patients suspected of having an airway disease (high pRatio ≤ 0.80). A false-positive by the PiKo-6 spirometry test could be the result of reversible airflow obstruction (i.e., asthma). The PiKo-6 spirometry cannot rule out asthma and should not be used to preselect patients at risk for asthma. We recommend future screening studies to either focus on asthma or COPD, as both diseases have different diagnostic procedure. Screening for COPD in community pharmacies does not require reversibility testing. Thus, it is more practical to screen for COPD than asthma in a community pharmacy setting.

5.7 Conclusion

Although pre-BD PiKo-6 device significantly underestimated pFEV₁, on average, the pRatio correlates well with standard spirometry FEV₁/FVC data. The PiKo-6 could be used as a simple screening tool to preselect subjects for a full diagnostic spirometry. However, the PiKo-6 should not replace standard diagnostic spirometry. It is proposed that portable spirometry combined with questionnaires may play a role in screening patients with SOB symptoms in community pharmacies that may benefit from early physician diagnosis and appropriate

management. Close cooperation between pharmacists, general practitioners, and pulmonary specialists is mandatory to confirm airflow limitation.

References

- Aaron, S., Vandemheen, K., Boulet, L., McIvor, R., FitzGerald, J., Hernandez, P., & ... Fergusso, D. (2008). Overdiagnosis of asthma in obese and nonobese adults [corrected] [published erratum appears in CMAJ 2008 Dec 2;179(12):1301]. *CMAJ: Canadian Medical Association Journal*, 179(11), 1121-1131.
- American College of Preventive Medicine. Indoor asthma triggers. Retrieved from http://c.ymcdn.com/sites/www.acpm.org/resource/resmgr/timetools-files/timetool_indoorasthma-trigger.pdf?hhSearchTerms=%22indoor+and+asthma+and+triggers%22
- American Thoracic Society and European Respiratory Society. (2004). Standards for the diagnosis and management of patients with COPD.
- Arnold, J. M., Liu, P., Demers, C., Dorian, P., Giannetti, N., Haddad, H., . . . Canadian Cardiovascular Society. (2006). Canadian cardiovascular society consensus conference recommendations on heart failure 2006: Diagnosis and management. *The Canadian Journal of Cardiology*, 22(1), 23-45.
- Bellia, V., Sorino, C., Catalano, F., Augugliaro, G., Scichilone, N., Pistelli, R., . . . Antonelli-Incalzi, R. (2008). Validation of FEV6 in the elderly: Correlates of performance and repeatability. *Thorax*, 63(1), 60-66.
- Bemt, L., Wouters, B. C. W., Grootens, J., Denis, J., Poels, P. J., & Schermer, T. R. (2014). Diagnostic accuracy of pre-bronchodilator FEV 1 /FEV 6 from microspirometry to detect

airflow obstruction in primary care: A randomised cross-sectional study. *Npj Primary Care Respiratory Medicine*, 24

Bland , M. (2000). *An introduction to medical statistics*. Oxford, NY: Oxford University Press.

Bland, J. M., & Altman, D. G. (1986). Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*, 1(8476), 307-310.

Braman, S. S. (2006). The global burden of asthma. *Chest*, 130(1 SUPPL.), 4S; 12S.

Bui, A. L., Horwich, T. B., & Fonarow, G. C. (2011). Epidemiology and risk profile of heart failure. *Nature Reviews Cardiology*, 8(1), 30-41.

Canadian Institute for Health Information. (2008). Health indicators. Retrieved from https://secure.cihi.ca/free_products/HealthIndicators2008_ENGweb.pdf

Cawley, M. J., Pacitti, R., & Warning, W. (2011). Assessment of a pharmacist-driven point-of-care spirometry clinic within a primary care physicians office. *Pharmacy Practice*, 9(4), 221-227.

Coates, A. L., Graham, B. L., McFadden, R. G., McParland, C., Moosa, D., Provencher, S., & Road, J. (2013). Spirometry in primary care. *Canadian Respiratory Journal*, 20(1), 13-22.

Currow, D. C., Plummer, J. L., Crockett, A., & Abernethy, A. P. (2009). A community population survey of prevalence and severity of dyspnea in adults. *Journal of Pain and Symptom Management*, 38(4), 533-545.

- Decramer, M., Janssens, W., & Miravittles, M. (2012). Chronic obstructive pulmonary disease. *The Lancet*, 379(9823), 1341-1351.
- Elbehairy, A. F., Webb, K. A., Neder, J. A., & O'Donnell, D. E. (2013). Should mild COPD be treated? evidence for early pharmacological intervention. *Drugs*, 73(18), 1991-2001.
- Evans, J., Chen, Y., Camp, P., Bowie, D., and McRae, L. (2014). Estimating the prevalence of COPD in canada: Reported diagnosis versus measured airflow obstruction.
- Ferguson, G., Enright, P., Buist, S., and Higgins, M. Office spirometry for lung health assessment in adults* A consensus statement from the national lung health education program. *National Lung Health Education Program*,
- Fleiss J. The Design and Analysis of Clinical Experiments. New York: John Wiley & Sons, 1986
- Frith, P., Crockett, A., Beilby, J., Marshall, D., Attewell, R., Ratnanesan, A., & Gavagna, G. (2011). Simplified COPD screening: Validation of the PiKo-6(registered trademark) in primary care. *Primary Care Respiratory Journal*, 20(2), 190-198.
- Fuller, L., Conrad, W. F., Heaton, P. C., Panos, R., Eschenbacher, W., & Frede, S. M. (2012). Pharmacist-managed chronic obstructive pulmonary disease screening in a community setting. *Journal of the American Pharmacists Association*, 52(5), e59; e66.
- Gershon, A. S., Guan, J., Wang, C., & To, T. (2010). Trends in asthma prevalence and incidence in ontario, canada, 1996-2005: A population study. *American Journal of Epidemiology*, 172(6), 728-736.

- Gershon, A. S., Hwee, J., Croxford, R., Aaron, S. D., & To, T. (2014). Patient and physician factors associated with pulmonary function testing for COPD : A population study. *Chest*, 145(2), 272-281.
- Glindmeyer, H. W., Jones, R. N., Barkman, H. W., & Weill, H. (1987). Spirometry: Quantitative test criteria and test acceptability. *American Review of Respiratory Disease*, 136(2), 449-452.
- Global Initiative for Asthma. (2014). Global strategy for asthma management and prevention. Retrieved from www.ginasthma.org
- Global Initiative for Chronic Obstructive Lung Disease. (2014). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Retrieved from http://www.goldcopd.com/uploads/users/files/GOLD_Report_2014_Oct30.pdf
- Hueston, W. (2002). *20 common problems in respiratory disorders* McGraw-Hill Professional.
- Jia, C. E., Zhang, H. P., Lv, Y., Liang, R., Jiang, Y. Q., Powell, H., . . . Wang, G. (2013). The asthma control test and asthma control questionnaire for assessing asthma control: Systematic review and meta-analysis. *Journal of Allergy and Clinical Immunology*, 131(3), 695-703.
- Jing, J. Y., Huang, T. C., Cui, W., Xu, F., & Shen, H. H. (2009). Should FEV1/FEV6 replace FEV1/FVC ratio to detect airway obstruction? A metaanalysis. *Chest*, 135(4), 991-998. doi:10.1378/chest.08-0723; 10.1378/chest.08-0723

- Kaufmann, M., Hartl, S., Geyer, K., Breyer, M. K., & Burghuber, O. C. (2009). Measuring FEV(6) for detecting early airway obstruction in the primary care setting. quality and utility of the new PiKo-6 device. *Respiration; International Review of Thoracic Diseases*, 78(2), 161-167. doi:10.1159/000197466; 10.1159/000197466
- Lee, T. A., Bartle, B., & Weiss, K. B. (2006). Spirometry use in clinical practice following diagnosis of COPD. *Chest*, 129(6), 1509-1515.
- Levy, D., Kenchaiah, S., Glarson, M., Benjamin, E. J., J.kupka, M., Ho, K. K. L., . . . Vasan, R. S. (2002). Long-term trends in the incidence of and survival with heart failure. *New England Journal of Medicine*, 347(18), 1397-1402.
- Levy, M. L., Quanjer, P. H., Booker, R., Cooper, B. G., Holmes, S., & Small, I. R. (2009). Diagnostic spirometry in primary care: Proposed standards for general practice compliant with american thoracic society and european respiratory society recommendations. *Primary Care Respiratory Journal*, 18(3), 130-147.
- Lin, H. -, Murray, M., Cohen, T., Colijn, C., & Ezzati, M. (2008). Effects of smoking and solid-fuel use on COPD, lung cancer, and tuberculosis in china: A time-based, multiple risk factor, modelling study. *The Lancet*, 372(9648), 1473-1483.
- Lloyd-Jones, . (2011). Erratum: Heart disease and stroke statistics-2010 update: A report from the american heart association (circulation (2010) 121 (e46-e215)). *Circulation*, 124(16), e425.

- Mason RJ, Broaddus VC, Martin TR, et al., (2010). *Murray and nadel's textbook of respiratory medicine* (5th ed.). Philadelphia, PA: Elsevier Saunders.
- McKelvie, R. S., Moe, G. W., Ezekowitz, J. A., Heckman, G. A., Costigan, J., Ducharme, A., . . . Sussex, B. (2013). The 2012 canadian cardiovascular society heart failure management guidelines update: Focus on acute and chronic heart failure. *Canadian Journal of Cardiology*, 29(2), 168-181.
- McMurray, J. J. V., Petrie, M. C., Murdoch, D. R., & Davie, A. P. (1998). Clinical epidemiology of heart failure: Public and private health burden. *European Heart Journal*, 19(SUPPL. P), P9; P16.
- Meek, P. M., Schwartzstein, R. M., Adams, L., Altose, M. D., Breslin, E. H., Carrieri-Kohlman, V., . . . Titler, M. (1999). Dyspnea: Mechanisms, assessment, and management: A consensus statement. *American Journal of Respiratory and Critical Care Medicine*, 159(1), 321-340.
- Midodzi, W. K., Mayers, I., Vethanayagam, D., Rowe, B., Chan, M., Nilsson, C., . . . Tsuyuki, R. T. (2010). Investigation of the epidemiology of shortness of breath (EPISOB)-a public health approach. *American Journal of Respiratory and Critical Care Medicine*, 181(1)
- Mittmann, N., Kuramoto, L., Seung, S. J., Haddon, J. M., Bradley-Kennedy, C., & FitzGerald, J. M. (2008). The cost of moderate and severe COPD exacerbations to the canadian healthcare system. *Respiratory Medicine*, 102(3), 413-421.

- Miller, M. R., Hankinson, J., Brusasco, V., Burgos, F., Casaburi, R., Coates, A., . . . ATS/ERS Task Force. (2005). Standardisation of spirometry. *The European Respiratory Journal*, 26(2), 319-338. doi:26/2/319.
- Moreira, G. L., Manzano, B. M., Gazzotti, M. R., Nascimento, O. A., Perez-Padilla, R., Menezes, A. M. B., & Jardim, J. R. (2014). PLATINO, a nine-year follow-up study of COPD in the city of sao paulo, brazil: The problem of underdiagnosis. *Jornal Brasileiro De Pneumologia*, 40(1), 30-37.
- National Heart, Lung, and Blood Institute. (2014). What is pulmonary hypertension?. Retrieved from <http://www.nhlbi.nih.gov/health/health-topics/topics/pah>
- National Lung Health Education Program. (2012). Checklist for compliance with NLHEP guidelines for office spirometers. Retrieved from <http://www.nlhep.org/Documents/srp-checklist.pdf>
- Nwagha, U., Iyare, E., Anyaehie, U., Onyedum, C., Okereke, C., Ajuzieogu, O., . . . Oguanuo, T. (2014). Forced expiratory volume in 6 s (FEV6) and FEV1/FEV6 values as a viable alternative for forced vital capacity (FVC) and FEV1/FVC values during pregnancy in south east nigeria: A preliminary study. *Annals of Medical and Health Sciences Research*, 4(4), 516-521. doi:10.4103/2141-9248.139294; 10.4103/2141-9248.139294
- Ober, C., & Yao, T. -. (2011). The genetics of asthma and allergic disease: A 21st century perspective. *Immunological Reviews*, 242(1), 10-30.

Omachi, T. A., Iribarren, C., Sarkar, U., Tolstykh, I., Yelin, E. H., Katz, P. P., . . . Eisner, M. D.

(2008). Risk factors for death in adults with severe asthma. *Annals of Allergy, Asthma and Immunology*, 101(2), 130-136.

Parshall, M. B., Schwartzstein, R. M., Adams, L., Banzett, R. B., Manning, H. L., Bourbeau,

J., . . . O'Donnell, D. E. (2012). An official american thoracic society statement: Update on the mechanisms, assessment, and management of dyspnea. *American Journal of Respiratory and Critical Care Medicine*, 185(4), 435-452.

Peacock, A. J., Murphy, N. F., McMurrey, J. J. V., Caballero, L., & Stewart, S. (2007). An

epidemiological study of pulmonary arterial hypertension. *European Respiratory Journal*, 30(1), 104-109.

Perez-Padilla, R., Wehrmeister, F. C., Celli, B. R., Lopez-Varela, M. V., Montes de Oca, M.,

Muino, A., . . . Pertuze, J. (2013). Reliability of FEV1/FEV6 to diagnose airflow obstruction compared with FEV1/FVC: The PLATINO longitudinal study. *Plos One*, 8(8)

Ponka, D., & Kirlew, M. (2007). Top 10 differential diagnoses in family medicine: Dyspnea.

Canadian Family Physician, 53(8), 1333.

Public Health Agency of Canada. (2009). Tracking heart disease and stroke in canada. Retrieved

from <http://www.phac-aspc.gc.ca/publicat/2009/cvd-avc/pdf/cvd-avs-2009-eng.pdf>

Public Health Agency of Canada. (2012). Fast facts about chronic obstructive pulmonary disease

(COPD) 2011. Retrieved from <http://www.phac-aspc.gc.ca/cd-mc/publications/copd-mpoc/ff-rr-2011-eng.php>

Public Health Agency of Canada. (2007). Life and breath: Respiratory disease in Canada.

Retrieved from <http://www.phac-aspc.gc.ca/publicat/2007/lbrdc-vsmrc/index-eng.php>

Qaseem, A., Wilt, T. J., Weinberger, S. E., Hanania, N. A., Criner, G., van der Molen, T., . . .

Shekelle, P. (2011). Disease: A clinical practice guideline update from the American college of physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. *Annals of Internal Medicine*, 155(3), 179-191.

Rank, M. A., Volcheck, G. W., Li, J. T. C., Patel, A. M., & Lim, K. G. (2008). Formulating an effective and efficient written asthma action plan. *Mayo Clinic Proceedings*, 83(11), 1263-1270.

Rehm, J., Gnam, W., Popova, S., Baliunas, D., Brochu, S., Fischer, B., . . . Taylor, B. (2007).

The costs of alcohol, illegal drugs, and tobacco in canada, 2002. *Journal of Studies on Alcohol and Drugs*, 68(6), 886-895.

Robinson, C. L., Baumann, L. M., Romero, K., Combe, J. M., Gomez, A., Gilman, R. H., . . .

Checkley, W. (2011). Effect of urbanisation on asthma, allergy and airways inflammation in a developing country setting. *Thorax*, 66(12), 1051-1057.

Rowe, B. H., Villa-Roel, C., Abu-Laban, R. B., Stenstrom, R., Mackey, D., Stiell, I. G., . . .

Young, B. (2010). Admissions to canadian hospitals for acute asthma: A prospective, multicentre study. *Canadian Respiratory Journal*, 17(1), 25-30.

- Saad, N., Seden, M., Metz, K., and Bourbeau, K. (2014). Early COPD diagnosis in family medicine practice: How to implement spirometry? *International Journal of Family Medicine*,
- Sansores, R. H., Ramirez-Venegas, A., Hernandez-Zenteno, R., Mayar-Maya, M. E., Perez-Bautista, O. G., & Velazquez Uncal, M. (2013). Prevalence and diagnosis of chronic obstructive pulmonary disease among smokers at risk. A comparative study of case-finding vs. screening strategies. *Respiratory Medicine*, 107(4), 580-586.
- Sears, M. R. (2014). Trends in the prevalence of asthma. *Chest*, 145(2), 219-225.
- Shiber, J. R., & Santana, J. (2006). Dyspnea. *Medical Clinics of North America*, 90(3), 453-479.
- Sichletidis, L., Spyros, D., Papaioannou, M., Chloros, D., Tsotsios, A., Tsagaraki, V., & Haidich, A. -. (2011). A combination of the IPAG questionnaire and PiKo-6(registered trademark) flow meter is a valuable screening tool for COPD in the primary care setting. *Primary Care Respiratory Journal*, 20(2), 184-189.
- Solidoro, P., Braid, F., Baratta, F., Bagnasco, D., Esposito, R., Aggeri, M., & Brusa, P. (2013). FEV6 assessment in spirometric abnormalities screening: The first population-based study in Italian pharmacies. *Panminerva Medica*, 55(1), 87-92.
- Spyros, D., Chloros, D., & Sichletidis, L. (2012). Diagnosis of chronic obstructive pulmonary disease in the primary care setting. *Hippokratia*, 16(1), 17-22.
- Statistics Canada. (2011). Leading causes of death, by sex (both sexes). Retrieved from: <http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/hlth36a-eng.htm>

- Statistics Canada. (2013). Asthma, 2012. Retrieved from <http://www.statcan.gc.ca/pub/82-625-x/2014001/article/14015-eng.htm>
- Statistics Canada. (2013). Chronic obstructive pulmonary disease in Canadians, 2009 to 2011. Retrieved from <http://www.statcan.gc.ca/pub/82-625-x/2012001/article/11709-eng.htm>
- Stenton, C. (2008). The MRC breathlessness scale. *Occupational Medicine (Oxford, England)*, 58(3), 226-227.
- Suh, E. , Mandal, S., & Hart, N. (2013). Admission prevention in COPD: Non-pharmacological management. *BMC Medicine*, 11(1)
- The Conference Board of Canada. (2012). Cost risk analysis for chronic lung disease in Canada Retrieved from <http://www.conferenceboard.ca/e-library/abstract.aspx?did=4585>
- Theriault, L., Gregory, H., Goldfarb, D., Stonebridge, C., Bounajm, F. (2012). Cost risk analysis for chronic lung disease in Canada. [] *The Conference Board of Canada*,
- To, T., Stanojevic, S., Moores, G., Gershon, A. S., Bateman, E. D., Cruz, A. A., & Boulet, L. P. (2012). Global asthma prevalence in adults: Findings from the cross-sectional world health survey. *BMC Public Health*, 12, 204.
- Tsuyuki, R. T., Johnson, J. A., Teo, K. K., Simpson, S. H., Ackman, M. L., Biggs, R. S., . . . Taylor, J. G. (2002). A randomized trial of the effect of community pharmacist intervention on cholesterol risk management: The study of cardiovascular risk intervention by pharmacists (SCRIP). *Archives of Internal Medicine*, 162(10), 1149-1155.

- Tsuyuki, R. T., Sin, D. D., Sharpe, H. M., Cowie, R. L., Nilsson, C., Man, S. F., & Alberta Strategy to Help Manage Asthma (ASTHMA) Investigators. (2005). Management of asthma among community-based primary care physicians. *The Journal of Asthma : Official Journal of the Association for the Care of Asthma*, 42(3), 163-167.
- Vestbo, J., Edwards, L. D., Scanlon, P. D., Yates, J. C., Agusti, A., Bakke, P., . . . Rennard, S. I. (2011). Changes in forced expiratory volume in 1 second over time in COPD. *New England Journal of Medicine*, 365(13), 1184-1192.
- Vos, T., Flaxman, A. D., Naghavi, M., Lozano, R., Michaud, C., Ezzati, M., . . . Murray, C. J. (2012). Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: A systematic analysis for the global burden of disease study 2010. *The Lancet*, 380(9859), 2163-2196.
- Wada, H., Nakano, Y., Nagao, T., Osawa, M., Yamada, H., Sakaguchi, C., . . . Horie, M. (2010). Detection and prevalence of chronic obstructive pulmonary disease in a cardiovascular clinic: Evaluation using a hand held FEV(1)/FEV(6) meter and questionnaire. *Respirology (Carlton, Vic.)*, 15(8), 1252-1258. doi:10.1111/j.1440-1843.2010.01854.x; 10.1111/j.1440-1843.2010.01854.x
- Wahls, S. A. (2012). Causes and evaluation of chronic dyspnea. *American Family Physician*, 86(2), 173-180.
- Walters, J. A., Haydn Walters, E., Nelson, M., Robinson, A., Scott, J., Turner, P., & Wood-Baker, R. (2011). Factors associated with misdiagnosis of COPD in primary care. *Primary Care Respiratory Journal*, 20(4), 396-402.

World Health Organization. (2014). Bronchial asthma. Retrieved from

<http://www.who.int/mediacentre/factsheets/fs206/en/>

World Health Organization (2007). Global surveillance, prevention and control of chronic respiratory diseases: A comprehensive approach. Retrieved from

<http://www.who.int/gard/publications/GARD%20Book%202007.pdf?ua=1>

World Health Organization. (2008). Global alliance against chronic respiratory diseases.

Retrieved from http://www.who.int/gard/news_events/World_Health_Statistics_2008/en/

World Health Organization. (2013). Asthma. Retrieved from

<http://www.who.int/mediacentre/factsheets/fs307/en/index.html>

World Health Organization. (2014). Asthma: Definition. Retrieved from

<http://www.who.int/respiratory/asthma/definition/en/>

APPENDIX 1: Patient Interview Forms

<h2 style="margin: 0;">EpiSOB</h2> <p style="margin: 0;"><i>Investigation of the Epidemiology of Shortness of Breath – A Public Health Approach</i></p>										
Study ID #	<div style="border: 1px solid black; width: 30px; height: 20px;"></div>	<div style="border: 1px solid black; width: 30px; height: 20px;"></div>	-	<div style="border: 1px solid black; width: 30px; height: 20px;"></div>	<div style="border: 1px solid black; width: 30px; height: 20px;"></div>	<div style="border: 1px solid black; width: 30px; height: 20px;"></div>	Patient Initials	<div style="border: 1px solid black; width: 30px; height: 20px;"></div>	<div style="border: 1px solid black; width: 30px; height: 20px;"></div>	<div style="border: 1px solid black; width: 30px; height: 20px;"></div>
	Site Number			Patient Number				First	Middle	Last

Date of Interview / / ☐ Not done
 dd mm yyyy

If not done, complete signature/date block → Fax page 1 only to *EPICORE* Centre

Form completed by _____ Signature _____ Date ____ / ____ / ____
 (please print name) dd mm yyy

Demographics

Date of Birth / /
 dd mm yyyy

Sex ☐ Male ☐ Female

Postal Code _____

Marital Status (check one only)

- ☐ Single (*never married*)
 ☐ Separated
☐ Currently married
 ☐ Divorced
☐ Common Law/living with a partner
 ☐ Widowed

Highest level of education (check one only)

- ☐ Less than Grade XII
 ☐ Post secondary certificate/diploma/degree
☐ High school diploma
 ☐ Not stated
☐ Some post secondary

Ethnicity (check all that apply)

- ☐ Caucasian
 ☐ South Asian (*e.g. East Indian*)
☐ Black
 ☐ Middle Eastern
☐ Aboriginal
 ☐ Other, specify _____
☐ Hispanic
 ☐ Not stated
☐ Oriental

Drug Insurance Coverage (check all that apply)

- ☐ Private (*through employment, etc.*) ☐ Other, specify _____
- ☐ Government (*Child Benefit, Social Services,*
AISH, Gp 66, Gp 1, etc) ☐ None

Smoking History

- ☐ Current # of years _____ # of cigarettes/day _____
☐ Past # of years _____ # of cigarettes/day _____
☐ Never smoked

Second-hand exposure to cigarette smoke ☐ Yes ☐ No

If Yes, type (check all that apply)

- ☐ Childhood ☐ Adult ☐ Work-related/Other

EpiSOB <i>Investigation of the Epidemiology of Shortness of Breath – A Public Health Approach</i>									
Study ID #	<div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div>	<div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div>	-	<div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div>	<div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div>	<div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div>	<div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div>	<div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div>	<div style="border: 1px solid black; width: 20px; height: 20px; display: inline-block;"></div>
	Site Number			Patient Number		Patient Initials			
						First	Middle	Last	

Comorbidities/Patient-reported <i>(check all that apply)</i>			
<input type="checkbox"/> Allergies <input type="checkbox"/> Asthma (# of years _____) <input type="checkbox"/> Bronchitis, chronic <input type="checkbox"/> COPD (# of years _____) <input type="checkbox"/> Sinusitis or nasal polyps <input type="checkbox"/> Diabetes Type I <input type="checkbox"/> Diabetes Type II <input type="checkbox"/> CAD (<i>Ischemia, History of MI, Angina, CABG, PCI</i>) <input type="checkbox"/> Hypertension <input type="checkbox"/> None of the above	<input type="checkbox"/> High cholesterol <input type="checkbox"/> Heart Failure <input type="checkbox"/> Arrhythmias <input type="checkbox"/> A Fib/Flutter <input type="checkbox"/> Other arrhythmia <input type="checkbox"/> Malignancy <input type="checkbox"/> Osteoporosis <input type="checkbox"/> Depression <input type="checkbox"/> Current <input type="checkbox"/> Prior <input type="checkbox"/> Anxiety <input type="checkbox"/> Current <input type="checkbox"/> Prior <input type="checkbox"/> GERD/Heartburn <input type="checkbox"/> Anemia		

Family history (<i>1st degree</i>) of any of the following <i>(check all that apply)</i>	
<input type="checkbox"/> COPD/Other <input type="checkbox"/> Heart Disease <input type="checkbox"/> None of the above	<input type="checkbox"/> Asthma <input type="checkbox"/> Cystic Fibrosis

Medications <i>(currently using or started within the last 6 months)</i>					
Patient Report	Pharmacist Report	Name of Medication	Patient Report	Pharmacist Report	Name of Medication
<input type="checkbox"/>	<input type="checkbox"/>	ACE inhibitor	<input type="checkbox"/>	<input type="checkbox"/>	Anticholinergic, Long-Acting
<input type="checkbox"/>	<input type="checkbox"/>	ARB	<input type="checkbox"/>	<input type="checkbox"/>	Anticholinergic, Short-Acting
<input type="checkbox"/>	<input type="checkbox"/>	Beta Blocker	<input type="checkbox"/>	<input type="checkbox"/>	Short-Acting β_2
<input type="checkbox"/>	<input type="checkbox"/>	Calcium Channel Blocker	<input type="checkbox"/>	<input type="checkbox"/>	Long-Acting β_2
<input type="checkbox"/>	<input type="checkbox"/>	Diuretic	<input type="checkbox"/>	<input type="checkbox"/>	Inhaled Corticosteroid
<input type="checkbox"/>	<input type="checkbox"/>	Antidepressant	<input type="checkbox"/>	<input type="checkbox"/>	Steroid, Oral
<input type="checkbox"/>	<input type="checkbox"/>	Antipsychotic	<input type="checkbox"/>	<input type="checkbox"/>	Combination/Symbicort
<input type="checkbox"/>	<input type="checkbox"/>	Antihistamine	<input type="checkbox"/>	<input type="checkbox"/>	Combination/Advair
<input type="checkbox"/>	<input type="checkbox"/>	Other, specify _____	<input type="checkbox"/>	<input type="checkbox"/>	Theophylline
<input type="checkbox"/>	<input type="checkbox"/>	Other, specify _____	<input type="checkbox"/>	<input type="checkbox"/>	LTRA (<i>Singular</i>)
<input type="checkbox"/>	<input type="checkbox"/>	Other, specify _____	<input type="checkbox"/>	<input type="checkbox"/>	Ketotifen/Nedocromil

EpiSOB <i>Investigation of the Epidemiology of Shortness of Breath – A Public Health Approach</i>					
Study ID #	<input style="width: 20px; height: 20px;" type="text"/> <input style="width: 20px; height: 20px;" type="text"/>	–	<input style="width: 20px; height: 20px;" type="text"/> <input style="width: 20px; height: 20px;" type="text"/> <input style="width: 20px; height: 20px;" type="text"/>	Patient Initials	<input style="width: 30px; height: 20px;" type="text"/> <input style="width: 30px; height: 20px;" type="text"/> <input style="width: 30px; height: 20px;" type="text"/>
	Site Number		Patient Number		First Middle Last

Symptoms		
Index	Current	New York Heart Association Functional Classification <i>(check one only)</i>
<input type="checkbox"/>	<input type="checkbox"/>	1 No symptoms and no limitation in ordinary physical activity, (e.g. <i>shortness of breath when walking, climbing stairs</i>)
<input type="checkbox"/>	<input type="checkbox"/>	2 Mild symptoms (<i>mild shortness of breath and/or angina</i>) and slight limitation during ordinary activity.
<input type="checkbox"/>	<input type="checkbox"/>	3 Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (<i>20-100 meters</i>). Comfortable only at rest.
<input type="checkbox"/>	<input type="checkbox"/>	4 Severe limitations. Experiences symptoms even while at rest. Mostly bed-bound.
Index	Current	MRC Dyspnea Scale <i>(check one only)</i>
<input type="checkbox"/>	<input type="checkbox"/>	1 Not troubled by breathlessness except on strenuous exercise.
<input type="checkbox"/>	<input type="checkbox"/>	2 Short of breath when hurrying or walking up a slight hill.
<input type="checkbox"/>	<input type="checkbox"/>	3 Walks slower (<i>than contemporaries</i>) on level ground because of breathlessness or has to stop for breath when walking at own pace.
<input type="checkbox"/>	<input type="checkbox"/>	4 Stops for breath after walking about 100 meters or after a few minutes on level ground
<input type="checkbox"/>	<input type="checkbox"/>	5 Too breathless to leave the house, or breathless when dressing/undressing
Index	Current	Triggers <i>(check all that apply)</i>
<input type="checkbox"/>	<input type="checkbox"/>	Inhalant allergens (<i>cats, animals, dust mites, indoor mold, environmental</i>)
<input type="checkbox"/>	<input type="checkbox"/>	Occupational allergens (<i>refer to occupational trigger list</i>)
<input type="checkbox"/>	<input type="checkbox"/>	Irritants (<i>tobacco smoke, household chemicals, perfumes, pollution, wood-burning stove/fireplace</i>)
<input type="checkbox"/>	<input type="checkbox"/>	Other (<i>ASA/NSAIDs, endocrine, exercise, food/additives, GERD, respiratory infections, weather, etc.</i>)
Index	Current	Cough Symptoms <i>(check all that apply)</i>
<input type="checkbox"/>	<input type="checkbox"/>	Cough (<i>Daytime</i>) (# of days/week: Index <input style="width: 40px;" type="text"/> Current <input style="width: 40px;" type="text"/>)
<input type="checkbox"/>	<input type="checkbox"/>	Cough (<i>Nocturnal</i>) (# of days/week: Index <input style="width: 40px;" type="text"/> Current <input style="width: 40px;" type="text"/>)
<input type="checkbox"/>	<input type="checkbox"/>	Sputum production
<input type="checkbox"/>	<input type="checkbox"/>	Chest tightness
<input type="checkbox"/>	<input type="checkbox"/>	Wheeze
Index	Current	Other symptoms <i>(check all that apply)</i>
<input type="checkbox"/>	<input type="checkbox"/>	Edema
<input type="checkbox"/>	<input type="checkbox"/>	Fatigue
<input type="checkbox"/>	<input type="checkbox"/>	Bilateral ankle edema
<input type="checkbox"/>	<input type="checkbox"/>	Fever or flu symptoms at time of prescription
<input type="checkbox"/>	<input type="checkbox"/>	Absence from work or school (<i>due to shortness of breath</i>)
<input type="checkbox"/>	<input type="checkbox"/>	Most recent hospitalization or ER visit due to SOB (Date: <input style="width: 30px;" type="text"/> / <input style="width: 30px;" type="text"/> / <input style="width: 40px;" type="text"/>) <div style="text-align: right; font-size: small;">dd mm yyyy</div>

EpiSOB

Investigation of the Epidemiology of Shortness of Breath – A Public Health Approach

Study ID #

 -

Site Number

Patient Number

Patient Initials

First

Middle

Last

Work History

Not for Database

Present Occupation

Past Occupations

Occupational/Environmental History

Patient has been **regularly** exposed to (*check all that apply*)

- ☐ 1 Wood or cotton dust
☐ 2 Asbestos, silica, coal, talc
☐ 3 Manufacture of stone, glass, clay
☐ 4 Welding or pottery-making
☐ 5 Manufacture of plastics or rubber
☐ 6 Grains
☐ 7 Hooved farm animals (*sheep, goats, cattle, horses, pigs*)
☐ 8 Non-hooved farm animals (*chickens/turkeys*)
☐ 9 Hooved wild animals (*deer/moose*)
☐ 10 Animal hide or wool processing
☐ 11 Gases from formaldehyde, ammonia, chlorine
☐ 12 Paint, lacquer, hair spray, pesticide, acid, solvent
☐ 13 Latex gloves
☐ 14 Cigarette smoke
☐ 15 Landscaping or gardening soil
☐ 16 None of the above

Physical Exam

Weight kgHeight cmHeart Rate bpmRespiratory Rate / minBlood Pressure (*seated*) / mmHg

systolic

diastolic

Oxygen Saturation %

EpiSOB <i>Investigation of the Epidemiology of Shortness of Breath – A Public Health Approach</i>			
Study ID #	<div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div> – <div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div>	Patient Initials	<div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div> <div style="border: 1px solid black; width: 30px; height: 20px; display: inline-block;"></div>
	Site Number Patient Number		First Middle Last

Patient Awareness

Has your family physician ever given you a diagnosis for your SOB symptoms ☐ Yes ☐ No

If Yes, what diagnosis (*check all that apply*)

☐ Asthma ☐ COPD ☐ Heart Failure ☐ Other, specify _____

Have you ever seen a specialist for your SOB symptoms
(i.e. *Respirologist, Cardiologist, Internal Medicine, etc.*)

☐ Yes ☐ No

If Yes, approximate date of most recent visit [*enter month (mm) and year (yyyy)*]

01 / ____ / ____
mm yyyy

Were you referred by your family doctor

☐ Yes ☐ No

Were you given a diagnosis for your SOB symptoms

☐ Yes ☐ No

If Yes, what diagnosis (*check all that apply*)

☐ Asthma ☐ COPD ☐ Heart Failure ☐ Other, specify _____

Have you ever had any of the following tests for your SOB symptoms

Test/Procedure

If Yes, Approximate Date of Most Recent Test
(*enter month (mm) and year (yyyy)*)

PFT	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't know	01 / ____ / ____ mm yyyy
Chest X-ray	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't know	01 / ____ / ____ mm yyyy
Echo	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't know	01 / ____ / ____ mm yyyy
ECG	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't know	01 / ____ / ____ mm yyyy
Methacholine	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't know	01 / ____ / ____ mm yyyy
Other	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Don't know	01 / ____ / ____ mm yyyy

If Yes, specify _____

Form completed by _____ <small>(please print name)</small>	Signature _____	Date ____ / ____ / ____ <small>dd mm yyyy</small>
---	-----------------	--

Previous Test Results

EpiSOB <i>Investigation of the Epidemiology of Shortness of Breath – A Public Health Approach</i>																			
Study ID #										Patient Initials									

Previous Test Results (record most recent tests prior to study interview)

☐ No previous tests documented

Yes	No	N/D	Test	If Yes, Date (dd/mm/yyyy)
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Chest X-ray	____/____/____
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Echo	____/____/____
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	ECG	____/____/____
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Methacholine	____/____/____
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	PFT	____/____/____

Form completed by _____	Signature _____	Date ____/____/____
(please print name)		dd mm yyyy

EpiSOB Previous Test Results v1.doc
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19 February 2009

Fax completed forms to the EPICORE Centre (780) 492-6059 or 1-888-215-5474

Laboratory Results Form

Test Results

EpiSOB <i>Investigation of the Epidemiology of Shortness of Breath – A Public Health Approach</i>									
Study ID #	<input style="width: 20px; height: 20px;" type="text"/> <input style="width: 20px; height: 20px;" type="text"/>	-	<input style="width: 20px; height: 20px;" type="text"/> <input style="width: 20px; height: 20px;" type="text"/>		Patient Initials	<input style="width: 20px; height: 20px;" type="text"/> <input style="width: 20px; height: 20px;" type="text"/> <input style="width: 20px; height: 20px;" type="text"/>	First	Middle	Last

Ensure the results recorded below are dated ON or AFTER the date of the patient interview

BNP	Date (dd/mm/yyyy) ____/____/____	Result ____	pg/mL
-----	----------------------------------	-------------	-------

PFT	Date (dd/mm/yyyy) ____/____/____	
-----	----------------------------------	--

Spirometry			PRE		POST	
Value	Units	Reference	Actual	% Predicted	Actual	% Predicted
FVC	Litres	____.____	____.____	____	____.____	____
FEV ₁	Litres	____.____	____.____	____	____.____	____
FEV ₁ /FVC	%	____	____	____	____	____
PEF	L/sec	____.____	____.____	____	____.____	____
Lung Volumes						
VC	Litres	____.____	____.____	____		
TLC	Litres	____.____	____.____	____		
RV	Litres	____.____	____.____	____		
RV/TLC	%	____	____	____		
FRC PL	Litres	____.____	____.____	____		
Diffusion						
DLCO	ml/mmHg/min	____.____	____.____	____		
VA	ml/mmHg/min	____.____	____.____	____		
DLCO Adj for VA	ml/mmHg/min/L	____.____	____.____	____		

Chest X-ray	<input type="checkbox"/> Yes <input type="checkbox"/> No	If Yes, Date (dd/mm/yyyy) ____/____/____
-------------	--	--

Echo	<input type="checkbox"/> Yes <input type="checkbox"/> No	If Yes, Date (dd/mm/yyyy) ____/____/____
------	--	--

ECG	<input type="checkbox"/> Yes <input type="checkbox"/> No	If Yes, Date (dd/mm/yyyy) ____/____/____
-----	--	--

Methacholine	<input type="checkbox"/> Yes <input type="checkbox"/> No	If Yes, Date (dd/mm/yyyy) ____/____/____
--------------	--	--

Form completed by _____	Signature _____	Date ____/____/____
(please print name)		dd mm yyyy

EpiSOB

Investigation of the Epidemiology of Shortness of Breath – A Public Health Approach

Study ID #

 -

Site Number

Patient Number

Patient Initials

First

Middle

Last

 Date of Assessment ____ / ____ / ____
 dd mm yyyy

Directions:

1. Review PFT/BNP test results
2. Review **Patient Interview (history)** form
3. Complete **Adjudicator Diagnostic Assessment** form → Fax to EPICORE Centre

Diagnosis (based on laboratory data, history and symptoms)

Definite diagnosis of **COPD**(i.e. post-bronchodilator FEV_1 <80% predicted together with an FEV_1/FVC <0.70)☐ Yes ☐ No

If No, (check all that apply)

- ☐ Review of patient's symptoms/history for COPD completed
☐ Physician examination referral recommended

Definite diagnosis of **Asthma**(i.e. an increase in FEV_1 that is both >200 mL and 12% above pre-bronchodilator FEV_1)☐ Yes ☐ No

If No, recommend (check all that apply)

- ☐ Physician examination referral (if ACQ Score >0)
☐ Methacholine test (if no definite diagnosis of COPD)

Definite diagnosis of **Heart Failure** (BNP >500 pg/mL)☐ Yes ☐ No

If No, recommend:

- ☐ Physician examination referral recommended (if BNP 100-500 pg/mL)
☐ Normal/No further action required (if BNP <100 pg/mL)

Other diagnosis (eg. flu, croup)

☐ Yes ☐ No

If Yes, specify _____

For EPICORE Centre Use ONLY

Referral completed (check all that apply)

☐ Cardiologist☐ Respiriologist☐ Methacholine test

Form completed by _____

(please print name)

Signature _____

Date _____

dd mm yyyy

APPENDIX 2 Final Diagnosis Form

Final Diagnosis

<h2 style="margin: 0;">EpiSOB</h2> <p style="margin: 0;"><i>Investigation of the Epidemiology of Shortness of Breath – A Public Health Approach</i></p>												
Study ID #		Site Number	–	Patient Number		Patient Initials		First		Middle		Last

Date of Review / /
 dd mm yyyy

Final Diagnosis

Asthma ☐ Yes ☐ Probable ☐ No

If Yes or Probable, Diagnosis ☐ Diagnosis by guideline
 ☐ Physician diagnosis (Consensus panel)
 ☐ By airway hyperresponsiveness (Methacholine test)

COPD ☐ Yes ☐ Probable ☐ No

If Yes or Probable, Diagnosis ☐ Diagnosis by guideline
 ☐ Physician diagnosis (Consensus panel)

Heart Failure ☐ Yes ☐ Probable ☐ No

[illegible]

Other possibility ☐ Yes ☐ No

If Yes, Specify _____

☐ Protocol Incomplete

Not for Database

Comments: _____

Form completed by _____ Signature _____ Date ____ / ____ / ____
 (please print name) dd mm yyyy

EpiSOB Final Diagnosis v3.doc
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05 March 2010

Fax completed forms to the EPICORE Centre (780) 492-6059 or 1-888-215-5474

APPENDIX 3

Sample characteristics of the patients who volunteered to perform the PiKo-6 in community pharmacies compared with patients in the community who were recruited via the pharmacy records

Sample characteristics	PiKo-6 Volunteer (n=63)	Community Patients (n=175)	P-value
Age, yrs: Mean (SD)	53.9 (15.3)	45.22 (17.4)	0.001*
Sex, Male: n(%)	33 (52.4)	66 (37.7)	0.043*
Average BMI: Mean (SD)	31.92 (7.4)	29.93 (7.6)	0.077
Prior History of Asthma: n(%)	38 (60.3)	74.8 (61.7)	0.447
Prior History of COPD: n(%)	11 (17.5)	17 (9.7)	0.102
Caucasian: n(%)	47 (74.6)	160 (91.4)	0.001*
Smoking: n(%)	12 (19.0)	39 (22.3)	0.591
Allergies: n(%)	43 (68.3)	151 (86.3)	0.002*
Diabetes Type 2: n(%)	7 (11.1)	9 (5.1)	0.105
CAD: n(%)	5 (7.9)	12 (6.9)	0.775
Hypertension: n(%)	24 (38.1)	36 (20.6)	0.006*
High Cholesterol: n(%)	14 (22.2)	19 (10.9)	0.025*
Prior Heart Failure: n(%)	1 (1.6)	4 (2.3)	0.740
Current Depression: n(%)	16 (25.4)	60 (34.3)	0.194
MRC Dyspnea Scale: Mean (SD)	2.25 (1.12)	2.03 (0.93)	0.131
Prior PFT: n(%)	31 (49.2)	55 (31.4)	0.012*
Prior Chest x-ray: n(%)	30 (47.6)	102(58.3)	0.144
Prior Echo: n(%)	8 (12.7)	27 (15.4)	0.600
Prior ECG: n(%)	27 (42.9)	86 (49.1)	0.392
Prior Methacholine: n(%)	0 (0)	2 (1.1)	0.394
Previously given a diagnosis for SOB symptoms: n(%)	34 (54.0)	135(77.1)	0.001*
Systolic (mean)	125.92	123.64	0.450
Diastolic(mean)	76.79	77.61	0.651

*Significant Level $P < 0.05$.

SD: Standard Deviation, Yrs: years; COPD: Chronic Obstructive Pulmonary Disease; CAD: Coronary Artery Disease; MRC: Medical Research Council ; PFT: Pulmonary Function Test; Echo: Electrocardiogram; ECG: Echocardiography.